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# A STUDY OF THE DIURNAL VARIATIONS IN CIRCULATING LYMPHOCYTES IN NORMAL AND PSYCHOTIC SUBJECTS

FRED ELMADJIAN, M.S. AND GREGORY PINCUS, Sc.D.

*From the Laboratories of the Worcester Foundation for Experimental Biology and the Memorial Foundation for Neuro-Endocrine Research, Worcester State Hospital, Worcester, Massachusetts*

REPORT has been made of a diurnal variation in the urinary 17-ketosteroids of men, indicating (on an hourly basis) a minimal excretion at night and during the day a rise to a maximum, ordinarily occurring shortly after waking, and a decline thereafter (4, 6). The 17-ketosteroid output is taken as an index of adrenal secretion. Recently, Dougherty and White (2) have demonstrated that the administration of certain active adrenal cortical steroids will result in a notable decline of circulation blood lymphocytes in animals. We have data (unpublished) indicating a similar adrenal steroid effect in men. Investigation was therefore undertaken of the variations in circulating lymphocyte numbers as possible indices of adrenal cortical function in normal and in psychotic subjects.

## SUBJECTS AND METHODS

Six normal men and six normal women, working at the Worcester State Hospital, served as volunteer subjects, and blood counts were taken at intervals during a 24-hour period as indicated in Table 1. Samples from six psychotic patients in the hospital research ward were taken as indicated in Table 2. The schedule of the patients differs somewhat from that of the normal subjects, due to the difficulty of obtaining samples during sleep. An extra sample was therefore taken at 1:30 p.m. In each case blood was

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obtained from the ear lobe. During the waking hours each subject was required to sit quietly for fifteen minutes before the specimen was taken. The first few drops of blood following puncture were discarded, and a pipette sample was taken, then three smears. The diluting fluid for the

TABLE 1. ABSOLUTE LYMPHOCYTE COUNTS (CELLS PER CC.) IN 12 NORMAL SUBJECTS AT VARIOUS TIMES DURING THE DAY

| Subject No. | Sex | 3 a.m. | 8 a.m. | 11 a.m. | 4 p.m. | 10 p.m. | 3 a.m. |
|---|---|---|---|---|---|---|---|
| 1 | ♂ | 2560 | 1430 | 1610 | 1920 | 3340 | 2530 |
| 2 | ♂ | 2870 | 1440 | 1680 | 2560 | 2440 | 3320 |
| 3 | ♂ | 3500 | 2400 | 1930 | 2400 | 2710 | 2720 |
| 4 | ♂ | 2840 | 2250 | 2260 | 2650 | 2840 | 2950 |
| 5 | ♂ | 3720 | 2120 | 2360 | 3100 | 3810 | 4600 |
| 6 | ♂ | 3720 | 2640 | 2640 | 3400 | 2760 | 5050 |
| 7 | ♀ | 3670 | 2100 | 2660 | 3710 | 4180 | 5140 |
| 8 | ♀ | 4950 | 2750 | 1960 | 2630 | 3200 | 3900 |
| 9 | ♀ | 4000 | 2800 | 2280 | 3070 | 3250 | 3800 |
| 10 | ♀ | 4250 | 2880 | 2440 | 3060 | 4200 | 3720 |
| 11 | ♀ | 3450 | 3160 | 3000 | 2920 | 3650 | 4500 |
| 12 | ♀ | 5100 | 3450 | 3880 | 4050 | 5100 | 5570 |
| Means for | ♂ | 3201.7 | 2046.7 | 2080.0 | 2671.7 | 2983.3 | 3528.3 |
| Means for | ♀ | 4236.7 | 2856.7 | 2703.3 | 3240.0 | 3930.0 | 4438.3 |

pipettes was N/10 HCL, and Wright's stain was used for the differential staining.

For the total leucocyte count both sides of the counting chamber were used. Sufficient numbers of cells per pipette were counted to minimize counting error. For the differential counts all smears were required to be of uniform thickness and length. Cross sectional counts of two hundred cells per smear were made on the smears by the same individual to minimize

personal error. Variations in both total and differential counts compared favorably with the expectations indicated by Plum (7), Barnett (1), and Mainland *et al.* (3); for example, the standard deviation of the differential count on 25 sets of smears was 1.1 per cent, the expectation, with an average of 30 per cent lymphocytes, on usual criteria is 1.5 per cent.

TABLE 2. ABSOLUTE LYMPHOCYTE COUNTS (CELLS PER CC.) IN SIX PSYCHOTIC SUBJECTS

| Subject No. | Sex | Diagnosis | 8 a.m. | 11 a.m. | 1:30 p.m. | 4 p.m. | 10 p.m. |
|---|---|---|---|---|---|---|---|
| 1 | ♂ | Dementia praecox, simple | 1950 | 1850 | 1640 | 2720 | 2300 |
| 2 | ♂ | Undiagnosed psychosis | 1440 | 2100 | 1940 | 2440 | 2870 |
| 3 | ♂ | Dementia praecox, unclassified | 2440 | 2080 | 2200 | 2480 | 3500 |
| 4 | ♂ | Dementia praecox, paranoid chronic | 3100 | 3700 | 2620 | 3270 | 4300 |
| 5 | ♂ | Dementia praecox, paranoid | 2680 | 4300 | 4270 | 2800 | 2860 |
| 6 | ♂ | Dementia praecox, other types | 3250 | 3130 | 2930 | 4400 | 3400 |
| Means | | | 2476.7 | 2860.0 | 2600.0 | 3018.3 | 3205.0 |

## RESULTS

In Table 1 are presented the absolute lymphocyte counts taken on the twelve normal subjects. It is notable that in the case of every subject except *No. 11* a minimum count occurs at either 8 a.m. or 11 a.m. In all subjects the counts taken at 10 p.m. and 3 a.m. are greater than any recorded for the day. Moreover, there is a tendency for a regular rise in count from 3 a.m. on into the night. This is clearly demonstrable in the mean value for each sex, which are plotted in Figure 1.

The corresponding data for the six psychotic subjects are presented in Table 2. There is a tendency for an increasing count from morning to night, which is illustrated by the mean values plotted in Figure 1. The slope of the patients' curve of Figure 1 is clearly different from those of the normal subjects. The equations of the three curves and their statistical

constants are given in Table 3. The slope constant, $b$, for the patients is significantly different from that of the male controls (difference = 30.35, $S_D = 5.48$, $t = 5.54$, $P < 0.01$), whereas the slope constants of the control males and females do not differ significantly (difference = 12.16, $S_D = 5.60$, $t = 2.17$, $P > 0.05$.) Clearly, then, the diurnal rise in count ob-

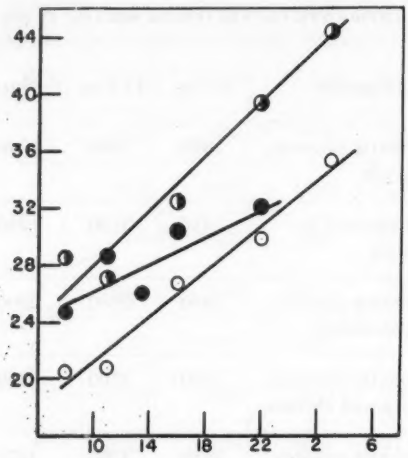


FIG. 1. The relation of mean lymphocyte count to time of day. Male controls: open circles; female controls: half circles; psychotic subjects: closed circles. Ordinate: lymphocyte number in hundreds; abscissae: time of day on a 24-hour scale. The data of the first 3 a.m. determination are omitted.

TABLE 3. THE EQUATIONS RELATING MEAN LYMPHOCYTE COUNT TO TIME OF DAY FOR THE THREE GROUPS OF SUBJECTS[1]

| Subjects | Linear regression | Standard error of estimate of $y$ | Standard error of $b$ |
|---|---|---|---|
| Normal females | $y = 1{,}902.98 + 91.29x$ | ±197.55 | ±4.85 |
| Normal males | $y = 1{,}332.92 + 79.12x$ | ±113.56 | ±2.79 |
| Psychotic males | $y = 2{,}122.39 + 48.77x$ | ±147.13 | ±4.72 |

[1] $y = a + bx$, where $y$ = mean lymphocyte count and $x$ = time of day.

served in the controls is much reduced in the psychotic subjects which, on the basis of the slope constants show a rate of increase some 40 per cent less than the controls.

The details of this difference in the nature of the diurnal variation are illustrated in Figures 2 and 3 in which are plotted the individual data for

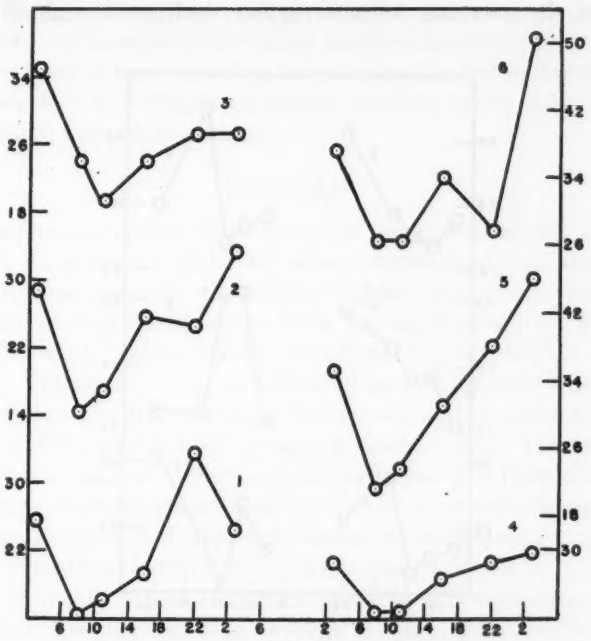


FIG. 2. Data on lymphocyte counts of six control male subjects plotted according to time of day. Each individual numbered as in Table 1. Ordinates: lymphocyte number in hundreds; abscissae: time of day on a 24-hour scale, in which midnight is 0 hour.

the male subjects. After an abrupt fall at waking, a rather consistent regular rise in count is shown for each subject except *No. 6*. His low 10 p.m. value may be due to a rather strenuous evening of bowling just preceding the count. Among the patients only *Nos. 2* and *3* show some regularity of increase.

## DISCUSSION

There appear to be three outstanding features of these data: (a) the abrupt morning drop followed by a rather regular increase in lymphocyte count in the normal men and women; (b) the parallel rate of increase in

both sexes despite the larger absolute count in the female subjects; (c) the irregular rate of increase in the psychotic subjects. It is interesting to note how these data fall into a reverse relationship with our findings on the urinary output of 17-ketosteroids. These are at a maximum in the morning hours. Since they presumably represent metabolites of corticosteroid secretions, we now have two indices indicating maximal adrenal cortex secretion in the morning with a regular decline throughout the day.

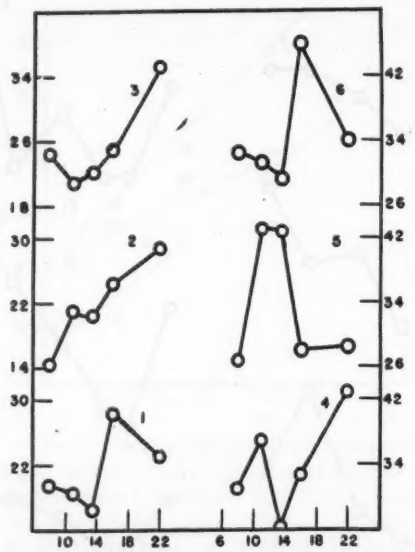


FIG. 3. Data on lymphocyte counts of six psychotic male subjects plotted according to time of day. Each individual numbered as in Table 2. Ordinates and abscissae as in Fig. 2.

Furthermore, we observed a decline of 17-ketosteroid output of approximately 60 per cent from waking to midnight, the lymphocyte increase from 8 a.m. to midnight is about 65 per cent.

It is generally recognized that the 17-ketosteroid output of men is greater than that of women, but with considerable overlapping (5). The absolute lymphocyte counts of our normal male and female subjects also overlap, but there tends to be a higher count in the female subjects. If the lymphocyte level is governed by the rate of corticosteroid secretion we should expect such a higher lymphocyte level in the female subjects.

The lymphocyte data for the psychotic subjects also accord with our findings on urinary 17-ketosteroid outputs. We have data (Pincus and Freeman, unpublished) indicating an average tendency in psychotic subjects for a flat diurnal curve, with certain individuals showing irregular curves or even reversals of the normal rhythm. The significance of these departures from normal indices of adrenal cortex function remains to be evaluated. We have here presented findings on six psychotic males, two of whom show no marked abnormality in the diurnal lymphocyte variation. A larger body of data including an inquiry as to day to day variations, correlated psychiatric findings and similar inquiries seems called for before a full evaluation may be attempted.

## SUMMARY

Blood lymphocyte counts were made for six normal males, six normal females, and six psychotic males at various intervals during the day and night. The normal subjects exhibited a regular increase in the absolute number of circulating lymphocytes from waking through the rest of the day and night, with a rather abrupt drop from sleep levels after waking in the morning. The female subjects exhibited an average count higher than that of the males, but the regression curve relating the count to the time of day did not differ significantly in slope in the two sexes. The mean curve for the psychotic subjects differed significantly in slope from those of the normal subjects, indicating a reduced rate of count increase throughout the day. Individual curves of the patients tended to show irregular changes in count, not encountered in the data for the normal subjects.

It is suggested that the diurnal increase in blood lymphocytes indicates declining adrenal cortex secretion through the day. This accords with the previous finding of a diurnal decrease in 17-ketosteroid output. Other correlations of lymphocyte count and 17-ketosteroid excretion are discussed.

## ACKNOWLEDGEMENTS

We are indebted to G. D. Searle and Co. for a grant in aid. Miss Muriel Ganzburg assisted ably in the technical work.

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# THE LYMPHOCYTE RESPONSE TO HEAT STRESS IN NORMAL AND PSYCHOTIC SUBJECTS

GREGORY PINCUS, Sc.D. AND FRED ELMADJIAN, M.S.

*From the Laboratories of the Worcester Foundation for Experimental Biology and the Memorial Foundation for Neuro-Endocrine Research, Worcester State Hospital, Worcester, Massachusetts*

IN ACCOMPANYING papers report is made of the diurnal rhythm of lymphocytosis (3) and of lymphocyte responses to psychomotor stress (5). In this paper we present data on the concentration of circulating lymphocytes found before and after exposures to heat and high humidity.

## SUBJECTS AND METHODS

Eleven healthy men ranging in age from 24 to 51 years were the control subjects and twenty-one psychotic subjects represented the patients. With four exceptions (*Subjects 12, 13, 14, 15*, Table 1) the patients had been admitted to the Worcester State Hospital within the previous six months and were chiefly men discharged from the military services.

At 1:30 p.m. for three successive days samples of blood were taken from the lobe of an ear of each subject as indicated in the previous paper. Then, ordinarily in groups of six in any one week, they entered unclothed a hot room, maintained at from 40.5° C. (105° F.) to 44.0° C. (112° F.) and at 85% to 95% relative humidity. Each subject consumed about a liter of water during his stay in the hot room, a rough equivalent of the sweat perspired. Subjects remained seated in the hot room for from 50 to 60 minutes, and on emerging were seated for 15 minutes when a second set of blood samples was taken. One hour and forty-five minutes later, after a shower and minor activity, a third set of samples was taken from a number of the subjects (see Table 1). These three samples are designated the pre-stress, stress, and post-stress samples respectively. Total leucocyte and differential counts were made as indicated in the preceding paper (3).

## RESULTS

In Table 1 we present the mean lymphocyte counts for each subject and the percentage change, taking the pre-stress value as 100. Each value of Table 1 is the mean of either two or three determinations involving either two or three hot room exposures.

It can be seen from Table 1 that despite considerable differences in the absolute counts between men each normal subject shows a stress (2:45

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TABLE 1. THE MEAN LYMPHOCYTE COUNTS OF MALE SUBJECTS IN THE HOT ROOM EXPERIMENTS

| (1) Subject No. | (2) Type | (3) (4) (5) Mean lymphocyte count (cells per cc.) at | | | (6) (7) Mean count as % of 1:30 p.m. value | |
|---|---|---|---|---|---|---|
| | | 1:30 p.m. | 2:45 p.m. | 4:30 p.m. | 2:45 p.m. | 4:37 p.m. |
| 1 | Normal | 2415 | 1716 | 1915 | 71.1 | 79.3 |
| 2 | Normal | 4216 | 3762 | 3398 | 89.3 | 80.6 |
| 3 | Normal | 5417 | 3870 | 4303 | 71.3 | 79.5 |
| 4 | Normal | 2700 | 2007 | 2667 | 75.4 | 98.7 |
| 5 | Normal | 2545 | 2040 | — | 80.2 | — |
| 6 | Normal | 3780 | 2280 | — | 60.4 | — |
| 7 | Normal | 3820 | 2900 | — | 76.0 | — |
| 8 | Normal | 2020 | 1420 | — | 70.3 | — |
| 9 | Normal | 3600 | 2650 | — | 73.7 | — |
| 10 | Normal | 4000 | 3550 | — | 88.7 | — |
| 11 | Normal | 2620 | 1950 | — | 74.5 | — |
| 12 | Dementia praecox, unclassified | 2408 | 3560 | 2519 | 147.9 | 104.6 |
| 13 | Dementia praecox, paranoid | 3728 | 4494 | 4313 | 120.5 | 116.7 |
| 14 | Dementia praecox, paranoid | 2249 | 2940 | 2394 | 130.7 | 107.5 |
| 15 | Dementia praecox, paranoid | 4940 | 4247 | 4442 | 86.0 | 90.0 |
| 16 | Dementia praecox, other types | 2724 | 3444 | 2099 | 126.4 | 77.0 |
| 17 | Dementia praecox, paranoid | 2744 | 3747 | 2711 | 131.5 | 98.8 |
| 18 | Dementia praecox, other types | 2619 | 3599 | 3156 | 137.4 | 120.5 |
| 19 | Dementia praecox, simple | 3109 | 3408 | 2473 | 109.6 | 79.6 |
| 20 | Dementia praecox, other types | 2217 | 2613 | 2097 | 127.9 | 94.6 |
| 21 | Undiagnosed psychosis | 2107 | 3370 | 2630 | 160.0 | 124.9 |
| 22 | Undiagnosed psychosis | 3838 | 4233 | 3758 | 110.3 | 97.9 |
| 23 | Dementia praecox, catatonic | 2480 | 3480 | 2173 | 140.2 | 87.7 |
| 24 | Dementia praecox, other types | 2675 | 3190 | — | 119.2 | — |
| 25 | Dementia praecox, paranoid | 2467 | 2407 | — | 97.6 | — |
| 26 | Dementia praecox, paranoid | 3130 | 3020 | — | 96.5 | — |
| 27 | Dementia praecox, paranoid | 2830 | 2983 | — | 105.4 | — |
| 28 | Dementia praecox, other types | 2575 | 3180 | — | 123.5 | — |
| 29 | Dementia praecox, hebephrenic | 3090 | 3900 | — | 126.2 | — |
| 30 | Undiagnosed psychosis | 2470 | 2775 | — | 112.4 | — |
| 31 | Undiagnosed psychosis | 3350 | 4075 | — | 121.6 | — |
| 32 | Undiagnosed psychosis | 1840 | 3230 | — | 175.6 | — |

p.m.) count that is lower than the pre-stress (1:30 p.m.) value. The patients, on the other hand, exhibit either a rise in count or no notable change with the exception of *No. 15*. In Figure 1 are plotted the stress counts taken as a per cent of the pre-stress values (from Table 1, column 6).

It is clear that the distribution of patients' values is quite different from that of the control subjects; the patients show a mean rise of 24.2 per

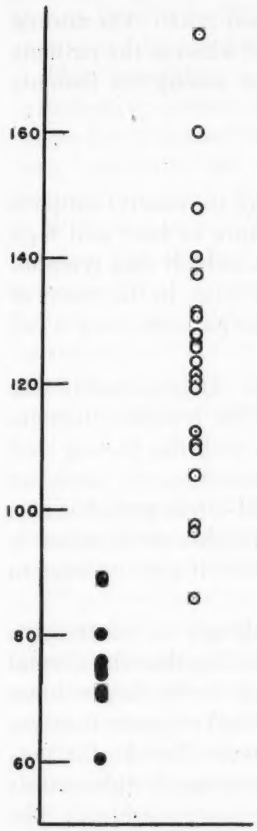


FIG. 1. The stress lymphocyte counts taken as a per cent of the pre-stress value in the eleven normal (closed circles) and the twenty-one psychotic (open circles) subjects. Data of column 6, Table 1.

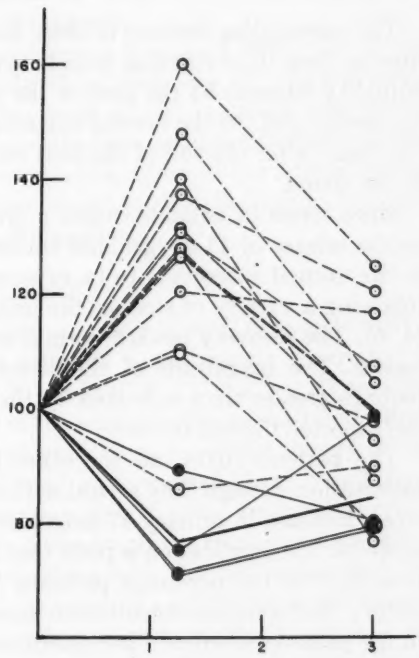


FIG. 2. The change of relative lymphocyte count with time in four normal subjects (solid lines) and twelve psychotic subjects (broken lines). The heavy solid and broken lines represent the mean per cent values for controls and patients respectively. Data from columns 6 and 7 of Table 1. Abscissa: time in hours; ordinate per cent.

cent normal subjects a mean drop of 24.5 per cent. The difference between these means is highly significant ($t=9.28$, $P<0.01$). The between-men variability is obviously greater among the patients, the standard deviation

of their distribution being 21.12 per cent compared with 8.26 per cent in the controls.

In Figure 2 are presented the percentage changes occurring with time in those subjects on whom post-stress counts were also taken. The normal subjects show a tendency to rise to the pre-stress level whereas the patients exhibit a fall in count. Again *No. 15* is the exception among the patients with his values falling well within the control group.

## DISCUSSION

The outstanding features of these data are: (a) all of the control subjects show a drop in circulating lymphocytes after exposure to heat and high humidity whereas 95 per cent of the patients fail to exhibit this lymphocytopenia, and (b) the normal subjects tend to show a rise in the count at two hours after the end of the heat stress whereas the patients show a fall in the count.

Since stress in animals causes a lymphocytopenia (2) presumably due to the release of 11-oxygenated corticosteroids (1), the lymphocytopenia in the normal subjects is to be expected. It accords with the finding that following a variety of stresses the urinary 17-ketosteroid output increases (4, 6). The recovery toward normal levels in the post-stress period is also logical. The magnitude of the stress decline in lymphocyte number is perhaps greater than indicated by the raw figures since it goes counter to the expected diurnal increase.

The patients' data, on the other hand, are strikingly in contrast to expectation, though they accord with our previous finding that the normal stress increase in urinary 17-ketosteroid output tends to fail in psychotic subjects. The implication is plain that the adrenocortical response to stress is at fault in the psychotic patients. We may, of course, invoke the possibility that a hemoconcentration accounts for the average lymphocytosis in the patients whereas a hemodilution occurs in the control subjects. The few checks that we have made to date show that there is no significant change in blood concentration in either type of subject. Furthermore sweat volumes in the two groups were the same. But if such a difference were genuine it would still offer a marked contrast between the mental patients and the normal men. The mean stress increase of 24.2 per cent in the patient group suggests a positive effect of the heat and high humidity. If these were men with a normal diurnal rhythm unaffected by the heat we would expect on the basis of the data of our preceding paper (3), to have a 5 per cent increase in lymphocyte count in the hour and fifteen minutes between the pre-stress and stress counts; in the psychotic subjects a mean $2\frac{1}{2}$ per cent increase was observed. But here we have a rise much outside

of this range.[1] If we consider that there are two processes responsible for the number of lymphocytes circulating in the blood, one concerned with lymphocyte production and a second with lymphocyte destruction then it may be that in the psychotic subjects the former process is particularly stimulated by the heat stress.

This possibility is not in disagreement with the post-stress fall in lymphocyte number, since one may postulate that with the removal of the stress the lymphocytosis stimulating factor is removed. Alternatively one may attribute this extremely consistent post-stress drop among the patients to a lag in the adrenocortical response.

With the short-time stress employed here it is entirely likely that we are dealing with the first stage of the adaptation syndrome (7) which involves adrenocortical hypersecretion as the result of the pituitary stimulation following stress. The inability of the patients to exhibit an adrenocortical response may be due to a block to secretory activity in the adrenal cortex itself or to a failure of typical pituitary secretion. We shall report later our experimental investigation of these alternatives.

## SUMMARY

Blood lymphocyte counts were taken on eleven normal men and twenty-one psychotic patients before and after 50 to 60 minute exposures to temperatures of from 40.5° C. (105° F.) to 44.0° C. (112° F.) at 85 per cent to 95 per cent relative humidity. All of the normal subjects exhibited a drop in lymphocyte count at the end of the hot room exposure; twenty of the twenty-one psychotic subjects exhibited an increased blood lymphocyte number after the heat exposure. The mean drop in count among the normal subjects was 24.5 per cent of the pre-stress level; the mean rise among the patients was 24.2 per cent of the pre-stress level. At two hours after the stress both the normal subjects and the patients exhibited a return toward the pre-stress levels. The stress lymphocytopenia of the controls is attributed to adrenocortical stimulation; such stimulation is not exhibited by 95 per cent of the patients.

## ACKNOWLEDGEMENTS

We are indebted to Mr. James Carlo for conducting the hot room exposures and to Miss Muriel Ganzburg for technical assistance. This investigation was aided by grants from G. D. Searle and Co.

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[1] Counts were taken on four patients (*No. 16* to *No. 19*) at the usual times on one day but without hot room exposure. The mean counts at 2:45 p.m. and 4:30 p.m. were 96.5 per cent and 108.0 per cent respectively of the 1:30 p.m. counts, whereas their corresponding values after the heat stress were 126.7 per cent and 99.6 per cent.

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# STRESSFUL PSYCHOMOTOR PERFORMANCE AND ADRENAL CORTICAL FUNCTION AS INDICATED BY THE LYMPHOCYTE RESPONSE

HUDSON HOAGLAND, PH.D.,[1] FRED ELMADJIAN, M.S., AND GREGORY PINCUS, SC.D.

*From the Worcester Foundation for Experimental Biology and the Memorial Foundation for Neuro-Endocrine Research, Worcester State Hospital, Worcester, Massachusetts*

IN PREVIOUS studies (7, 8) we have shown that the stress of prolonged pursuitmeter operations of healthy young men enhances the output of urinary 17-ketosteroids above their resting levels, and we have described relations between scoring ability in fatiguing pursuitmeter tests and the magnitude of steroid excretion. Anoxia produced by breathing air deficient in oxygen not only quantitatively reduces ability to maintain high pursuitmeter scores in an hour's test, but also greatly increases the output of 17-ketosteroids which are primarily of adrenal cortical origin.

Dougherty and White (1) have presented evidence (based on the administration of corticotrophin and adrenal cortical extracts) that a drop in the lymphocyte count results from the action of adrenal cortical hormones in animals. We have shown (2) that mice stressed by being tied down show a marked and progressive depression of the lymphocyte count during the stress which effect is absent if the adrenal glands are removed.

Following a study (6) of a group of 21 psychotic patients and 11 normal controls exposed to high temperatures and high humidities we have reported a marked **fall** in the relative lymphocyte counts in normal subjects and, interestingly enough, a **rise** in lymphocyte counts in the patients. Correspondingly the 17-ketosteroid excretion of the normals is enhanced by the heat stress, while that of the patients is, for the most part, enhanced only slightly, if at all, and may show a fall with the stress.

We have previously reported (7) that the 17-ketosteroid excretion is increased on the average some 60 per cent on rising in the morning above the night level for healthy young persons. Elsewhere we have reported a corresponding fall in the lymphocyte count for the morning hours as against the night levels. In psychotic patients we have found, in general, that this relation does not hold. The diurnal rhythm of 17-ketosteroid excretion tends to be flat and so does the diurnal rhythm of the lymphocyte count (3).

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[1] Fellow of the John Simon Guggenheim Memorial Foundation.

In the present paper we wish to describe the effects of pursuitmeter stress, with and without low oxygen administration, on lymphocyte counts and on 17-ketosteroid excretion in a group of six normal persons (three men, three women) and in three male psychotic patients.

## PROCEDURE

The apparatus used for producing stress and measuring its effects on performance was the Hoagland-Werthessen pursuitmeter. This apparatus has been described elsewhere (7). It consists of airplane stick and rudder pedal controls that operate a pointing rectangular light beam. At approximately eight feet in front of the operator an airplane model mounted on the end of a rod is caused to move in a thoroughly random and non-repeating fashion, banking to left and right and moving up and down. In the two "engine nacelles" of the model are photo-electric cells. The operator must "fly in tight formation" with this model by simultaneously bracketting both photo-electric cells with his rectangular beam of light. He is automatically scored for his ability to do this; a counter registers each time he slips off one or both cells with his pointing light, and clocks register his per cent time on target for any chosen interval.

In this way, for example, by taking five minute readings over a continuous run of an hour a curve of performance characteristic of the individual can be plotted. For practiced operators these curves show a decline characteristic of the individual during the test. A single numerical measure of fatigue can be had by dividing the mean score for the first half of a run into that for the second half. Thus, a fall of this ratio (the "fatigue ratio") below unity for a skilled operator is a measure of his fatiguing. For most people from seven to ten hours of practice are needed before the learning curve becomes flat, although, because of "transfer of learning," professional aviators usually show flat learning curves in from two to three hours. Army pilots who have used this apparatus say it is about as fatiguing as close formation flying under poor weather conditions.

In 25 of our 49 experiments the operator breathed air low in oxygen from a face mask. The mask was connected to a Tisot respirometer which at the start contained room air. Carbon dioxide was absorbed by a large soda-lime container in series with the mask and with a BaOH indicator bottle. Since the system was a closed one, the operator reduced the oxygen content during the run, so that in from 15 to 20 minutes he usually was breathing about 12 per cent $O_2$. Samples of air were withdrawn from the apparatus near the mask's inlet at frequent (usually 10 minute) intervals and analyzed for $O_2$ content in a Haldane-Henderson apparatus. When the desired level of oxygen was reached, a pressure valve to an oxygen tank was cracked open so as to admit oxygen in sufficient amount to keep the float of the

respirator bell at a constant level. In this way the experiment was analogous to that of a person flying an airplane up to approximately 15,000 feet in from 15 to 20 minutes, and then continuing to fly at that altitude for the remainder of the hour.

In 35 of the 49 experiments timed urine samples were collected as controls before the "flight," and urine samples were collected covering the hour of the "flight." Determinations of 17-ketosteroids were made on these samples by methods previously described, (5) and the change of excretion, in mg. per unit of time, due to the stress of the test was compared to the control sample.

Blood samples for determining lymphocytes were taken from the ear lobe during each of the 49 runs. The pre-test sample was taken after a 15 minute rest in sitting posture immediately before the test; and the test sample was taken after a 15 minute rest following the run. In 27 of the 49 tests four blood samples were taken; one, pre-test; one, five minutes before the end of the test; one, 15 minutes after the end of the test; and one, 90 minutes after the test. In three runs on the normal subject, *F. E.*, blood samples were taken every 20 minutes, so that the lymphocytes could be followed during the course of the runs. Absolute lymphocyte counts were made on the samples after the manner described elsewhere (3). Two samples for total leucocyte count were taken instead of one at each period, and the effects of the stress of the runs was determined.

The subjects were three normal men and three normal women employees of the Worcester State Hospital, two cooperative, chronic schizophrenic patients, and one cooperative patient diagnosed as having a psychopathic personality with psychosis. This last patient was well on the road to recovery at the time of the experiments, and was discharged from the hospital two months after their completion.

## RESULTS

In a previous study (7) we reported that the fatigue ratio is markedly modified by breathing low $O_2$, and that some persons show an appreciable decline in this ratio at $O_2$ tensions as low as that corresponding to 5,000 feet.

The subjects in these earlier experiments operated the pursuitmeter for two hours rather than for one, and the fatigue effects would therefore be expected to be more accentuated than they would be in tests of one hour. In our earlier series the subjects entered a room the air of which had been previously diluted to the desired oxygen content with nitrogen and thus their run started at essentially the same oxygen level as that of the finish. They thus were exposed to the low oxygen for 15 to 20 minutes longer in the first hour than they would be had they been made anoxic by the rebreathing apparatus used in our present series. It was therefore necessary

to establish performance curves for the hour tests with our new method of producing anoxia.

Figure 1 shows data from six runs. The three figures on the left are from

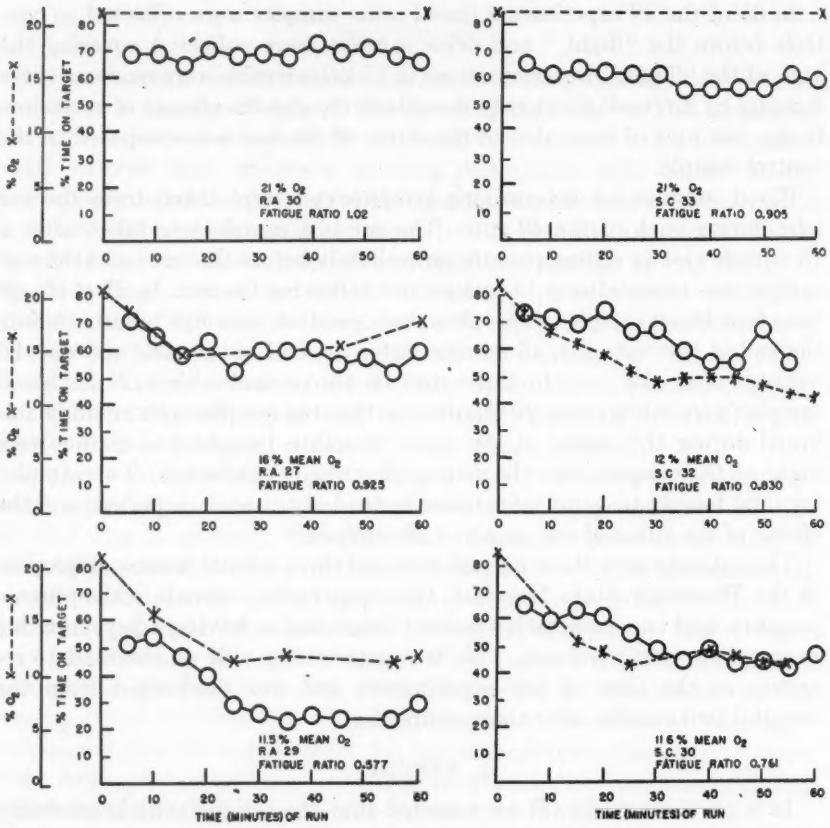


FIG. 1. Pursuitmeter scoring as a function of time at different oxygen levels.

The circles represent per cent time on target; the crosses are oxygen determinations (made with a Haldane-Henderson apparatus) on the inspired air. The "mean oxygen" values are those for the later flat portions of the curves.

The fatigue ratios vary with the inspired oxygen.

data obtained from the patient, *R. A.*, and the three figures on the right are from data from the normal person, *S. C.* The numbers after the initials on the figures refer to the number of the experiment on that individual. Thus, *S. C.* had had at least 30 hours of practice, and *R. A.* a minimum of 27 hours, so that learning is not a problem here.

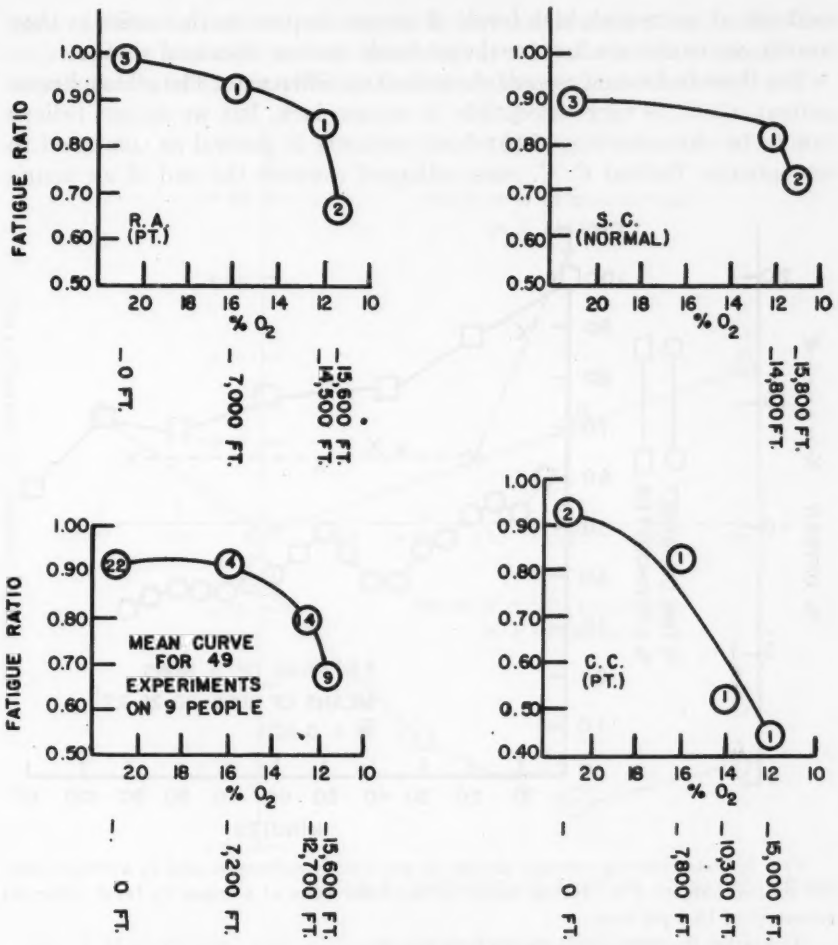


FIG. 2. Fatigue ratios for three individuals and for the group mean plotted against mean per cent $O_2$.

Numbers in the circles for the mean curve indicate the number of experiments averaged per point. Note marked individual differences. The points for the individuals are also averages for several runs each.

We see that the greater anoxia the greater the decline in the curves of performance and the lower the fatigue ratio.

Figure 2 shows plots of the fatigue ratio for three individuals against the per cent of $O_2$ breathed, and in the lower left hand corner is an average curve for the 49 experiments. This curve is essentially the same as that published by us previously except that the effects of anoxia are not in

evidence at quite such high levels of oxygen content in this series as they were in our earlier studies, for the probable reasons discussed above.

The three individual records show marked differences. The schizophrenic patient, *C. C.*, is very susceptible to oxygen lack, but we do not believe this to be characteristic of psychotic patients in general as compared to nonpatients. Patient *C. C.* once collapsed towards the end of an hour's

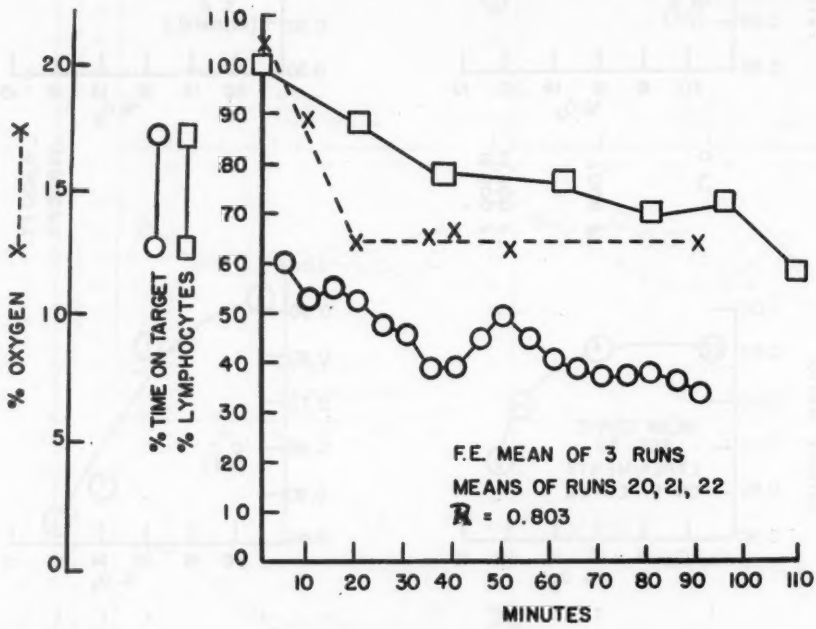


FIG. 3. Data showing average change in per cent lymphocytes and in average score for normal subject F.E. during three pursuitmeter runs at a mean $O_2$ level (after 20 minutes) of 13.5 per cent.

The letter *R* on the figure means fatigue ratio.

run at 12 per cent of $O_2$ although our other two patients showed as good a low oxygen tolerance as the normals.

Figure 3 demonstrates the typical lymphocyte decline during the progress of the tests. In this figure the pre-test lymphocyte level is taken as 100 per cent. The data are averages of three experiments. How much of the stress causing the drop is due to controlling the pursuitmeter and what part is due to low oxygen cannot be determined from this figure. We have used the pursuitmeter as a measure of stress response but it also produces stress itself with normal air, causing, in one hour, an average decline in the fatigue ratio of 10 per cent. The top left record of Fig. 1 showing a fatigue

ratio of 1.00 or greater is quite atypical. It occurs not more frequently than once in 20 runs. Later we will show, however, that there is no significant correlation between lymphocyte decline and oxygen level breathed per se,

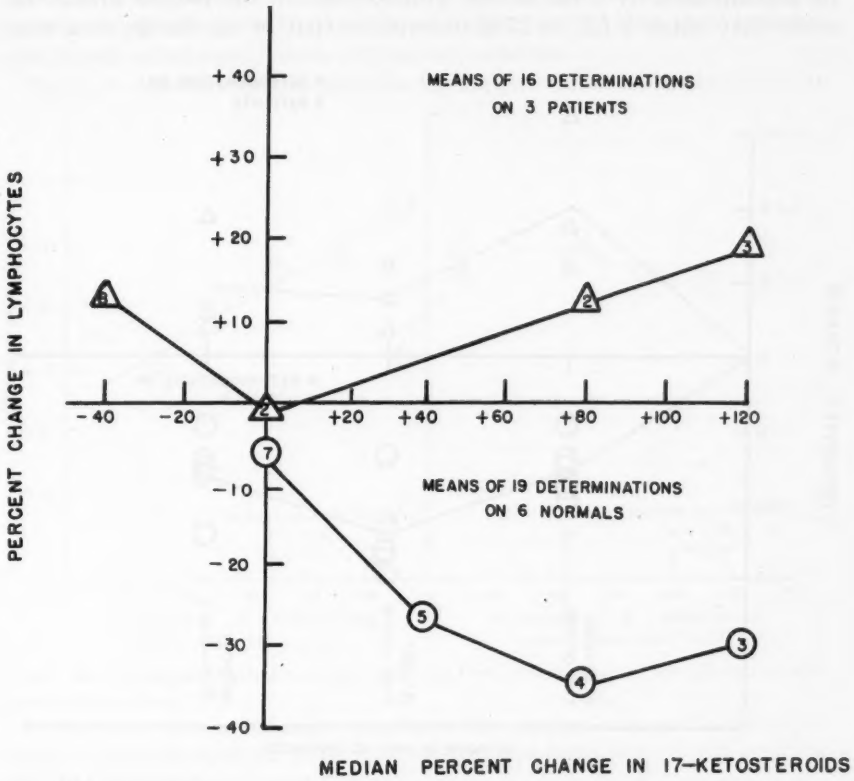


FIG. 4. Mean changes, with respect to resting levels (taken as 100 per cent), in relative lymphocyte counts, and, correspondingly plotted, 17-ketosteroid excretion for patients and controls when stressed by pursuitmeter operation.

Note consistent fall of lymphocytes with increased output of 17-ketosteroids in the normal group, and (in general) elevation of lymphocytes with stress accompanying enhanced 17-ketosteroid excretion in the patient group. The rise in 17-ketosteroid in the patient group is not consistent, as may be seen by the decline in stress 17-ketosteroids in eight of the 16 experiments and the unchanged (zero) values in two of them. Numbers in the plotted points refer to number of determinations averaged per point.

although there is a significant correlation between the fatigue ratio and the lymphocyte decline in our normal group.

Figure 4 shows the relationship between stress 17-ketosteroids (*i.e.*, the

per cent increase as a result of the runs over the pre-run levels) plotted against the per cent change in lymphocytes compared to pre-test levels. In the normal group the increase in stress 17-ketosteroid output is seen to be accompanied by a fall in the lymphocytes. In the patient group the stress may cause a fall in 17-ketosteroid output or no change or a rise.

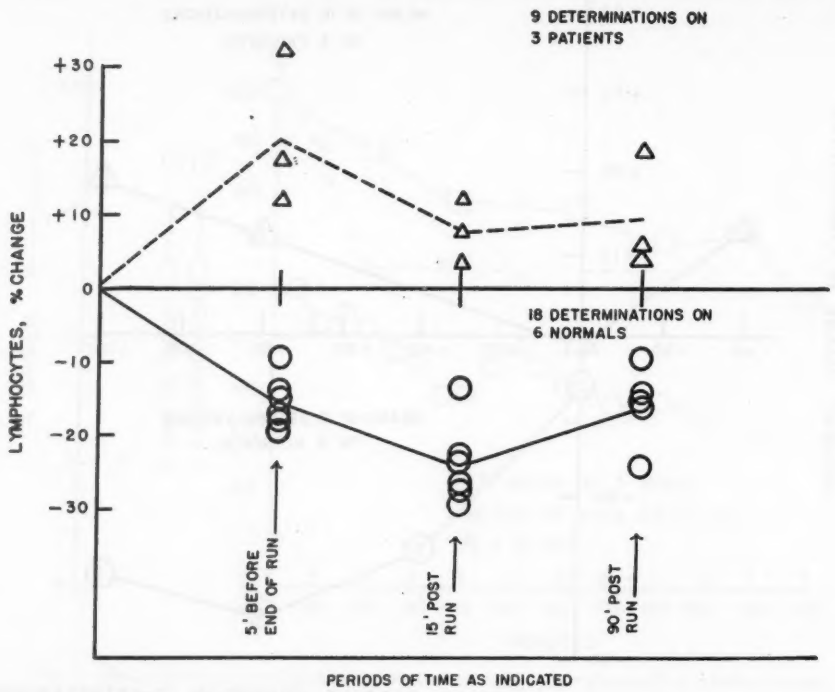


FIG. 5. Plot showing per cent increase over resting levels of lymphocytes with pursuitmeter stress in patients, and decrease in lymphocytes in stressed normals as compared to their resting levels.

Curves are drawn through average values. Note recovery trend after 90 minutes in the normals. Too few data are available on the patients for the shape of their curve to be significant.

Accompanying a rise or fall in 17-ketosteroids there is usually a rise in lymphocytes.

Figure 5 shows the per cent rise of stress lymphocytes over the resting levels in the patients, and the corresponding fall of stress lymphocytes in the normals as a function of time with respect to periods of the runs in 27 tests.

In the normal series the greater drop at 15 minutes post-test compared to the drop five minutes before the end of the test is noteworthy, as is the slowness of recovery of the depressed lymphocyte count 90 minutes after the tests. There are not enough data on the patients in this series to give meaning to the shape of their curve aside from noting that their lymphocyte counts consistently show a stress response rise.

Figure 6 shows correlation data for the fatigue ratios vs. the lymphocyte

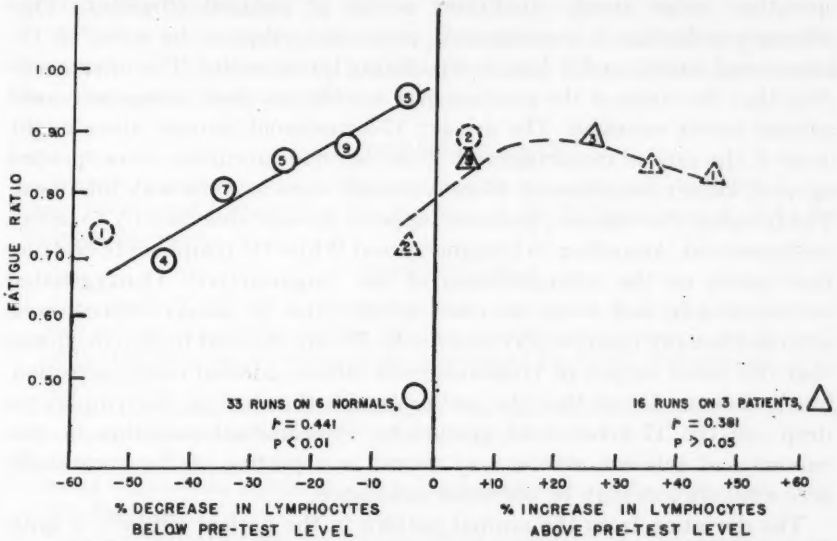


FIG. 6. Correlation between fatigue ratio and relative change of lymphocytes with pursuitmeter stress.

Circles are normals and triangles are patients. The numbers in the points refer to the number of tests averaged per point. Dashed circles and triangles are points involving only one or two tests.

The 49 experiments involved respired mean oxygen values as follows: 24 at 21 per cent; 3 at from 15–16 per cent; 3 at from 13–14 per cent; 11 at from 12.0 to 12.9 per cent; 8 at from 11.0 to 11.9 per cent.

changes. The correlation coefficient, $r$ value, of $-0.441$ for the normal group is significant ($P<0.01$); the $r$ of $+0.381$ for the patient group is not significant ($P>0.05$). There is a significant difference between the $r$ values of the normals and the patients (difference 0.822, $\delta_D=0.270$, $t=3.04$, $P<0.01$).

We also correlated the lymphocyte counts with per cent $O_2$ for the normal group and obtained $r=0.174$ which was not significant. It is thus interesting to note that the lymphocytes correlate significantly with the fatigue

ratio but not with the per cent oxygen breathed; *i.e.* the psychomotor behavior correlates with the lymphocyte changes better than does the external stimulus of the low oxygen per se.

## DISCUSSION

The data of this paper confirm our previous findings with other subjects under somewhat different conditions which showed that pursuitmeter operation under anoxic conditions occurs at reduced efficiency. This efficiency reduction is accompanied, in normal subjects, by a rise in 17-ketosteroid output and a drop in circulating lymphocytes. The inference is clear that the stress of the psychomotor activity involved causes increased adrenal cortex secretion. The urinary 17-ketosteroid increase alone might occur if the rate of metabolism of 17-ketosteroid precursors were speeded up or if kidney excretion of 17-ketosteroids were in some way increased. The lymphocyte response, however, appears accountable directly to active corticosteroid. According to Dougherty and White (1) lymphocyte destruction occurs on the administration of the "sugar-active" 11-oxygenated corticosteroids, and is not an effect attributable to desoxycorticosterone or to hormonally inactive corticosteroids. We are thus led to the conclusion that the stress output of 17-ketosteroids reflects adrenal cortex secretion, but it does not follow that the corticosteroids that induce the lymphocyte drop are the 17-ketosteroid precursors. Concomitant secretion of precursors and active hormone may occur, or a portion of the hormonally active substances may be precursor substance.

The deviation from the normal pattern in the patient subjects is noteworthy. Evidence has been presented indicating that under a variety of stresses psychotic subjects fail to exhibit the enhanced 17-ketosteroid excretion observed in normal controls (4). In the three patients of this series and in the patients subjected to heat stress, the lymphocyte response (presumably indicative of an adreno-cortical response) fails. Moreover, the nature of the patient's response is significantly in the opposite direction from that of the normal subjects. It is therefore suggested that in the mentally ill patients that we have examined there is a failure of normal adrenal cortex function in stress. If this can be established as generally typical of certain psychotic patients we have available a tool for the quantitative investigation of a deranged adaptive physiological function.

## SUMMARY

1. Effects on the efficiency of psychomotor performance of mixtures of air low in oxygen have been determined in one hour runs on six normal persons and three psychotic patients operating the Hoagland-Werthessen pursuitmeter.

2. The lymphocyte count falls with the stress of the experiments in normal persons and in general rises with the stress of the patients. In the normal group the lower the drop in lymphocytes the greater the decline in efficiency of performance as measured by decline in the "fatigue ratio" ($r = -0.441$, $P < 0.01$). The patients show a rise in lymphocytes correlated with the "fatigue ratio" ($r = +0.381$) but this is not significant ($P > 0.05$). The difference in $r$ value between patients and controls is, however, statistically significant.

3. In the normal group the stress is shown to increase the output of 17-ketosteroids as it lowers the lymphocyte count. The patients show anomolous changes in these variables.

ACKNOWLEDGEMENT

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# DIFFERENTIAL BLOOD COUNTS IN CERTAIN ADRENAL CORTICAL DISORDERS (CUSHING'S SYNDROME, ADDISON'S DISEASE AND PANHYPOPITUITARISM)[1]

F. A. DE LA BALZE, M.D.,[2] E. C. REIFENSTEIN, JR., M.D., AND FULLER ALBRIGHT, M.D.

*From the Medical Service of the Massachusetts General Hospital, and from the Department of Medicine of the Harvard Medical School, Boston, Massachusetts*

SELYE (10) and Dougherty and White (3) demonstrated in rats that the administration of pituitary adrenocorticotrophic hormone results in an increase in the absolute number of neutrophiles and a decrease in the absolute number of lymphocytes in the blood stream. Dougherty and White (3) obtained the same hematological alterations directly with corticosterone and with 11-dehydro, 17-hydroxycorticosterone (Compound E of Kendall), both of which are adrenal cortical compounds with a marked effect on carbohydrate metabolism, hence "sugar-hormones". Albright (1) has assembled the evidence that Cushing's syndrome is a manifestation of an hyperadrenocorticism-with-respect-to-the-"sugar-hormone". It seemed of interest, therefore, to determine whether a neutrophilic leukocytosis coupled with a lymphopenia occurs in patients with this disorder, and to compare the findings with those in primary panhypoadrenocorticism (Addison's disease) and in panhypoadrenocorticism secondary to panhypopituitarism (Simmonds' disease, pituitary dwarfism, *etc.*).

## METHODS

Ten patients with Cushing's syndrome, 20 patients with Addison's disease, and 20 patients with panhypopituitarism were used in this study, the diagnoses being carefully established by methods described elsewhere (1, 5, 9). A tabulation was made of the blood counts of the patients before any therapy had been administered, or after a considerable interval without therapy. When more than one determination was available, that with the lowest total leukocyte count was taken for the analysis. The blood determinations were made either by the routine laboratory technicians, or by members of the hospital house staff; no special hematological

[1] The expense of these studies was defrayed in part by grants from the Josiah Macy, Jr. Foundation and the Dazian Foundation.

[2] Research Fellow in Medicine, Harvard Medical School and Massachusetts General Hospital, 1944–1945; Instructor in Physiopathology and Clinical Diagnosis, University of Buenos Aires, 1945– .

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TABLE 1. COMPARISON OF LEUKOCYTE LEVELS IN CUSHING'S SYNDROME AND IN ADDISON'S DISEASE

| Patient | Unit number | Age | Sex | Total leukocytes per cu. mm. | Neutrophiles | | Lymphocytes | |
|---|---|---|---|---|---|---|---|---|
| | | | | | number per cu. mm. | per cent | number per cu. mm. | per cent |
| **Cushing's Syndrome** | | | | | | | | |
| *I.G.* | 350260 | 11 | f | 16,400 | 12,792 | 78 | 2,952 | 18 |
| *M.S.* | 347498 | 16 | f | 13,200 | 11,880 | 90 | 1,056 | 8 |
| *A.D.* | 499922 | 20 | f | 7,600 | 5,776 | 76 | 1,216 | 16 |
| *B.V.* | 74372 | 25 | f | 6,300 | 5,418 | 86 | 630 | 10 |
| *B.A.* | 467276 | 33 | f | 18,800 | 16,544 | 88 | 2,068 | 11 |
| *E.M.* | 305950 | 40 | f | 11,000 | 9,350 | 85 | 1,320 | 12 |
| *R.B.* | 3397 | 47 | f | 7,700 | 6,160 | 80 | 1,232 | 16 |
| *E.McL.* | 397957 | 49 | f | 11,600 | 8,700 | 75 | 2,088 | 18 |
| *T.B.* | 365392 | 51 | f | 9,600 | 8,928 | 93 | 384 | 4 |
| *A.P.* | 110122 | 56 | f | 11,450 | 7,443 | 65 | 2,061 | 18 |
| Average | | | | 11,365 | 9,299 | 81.6 | 1,500 | 13.1 |
| **Addison's Disease** | | | | | | | | |
| *H.M.* | 210582 | 21 | f | 9,200 | 5,244 | 57 | 3,404 | 37 |
| *H.H.* | 474131 | 26 | f | 8,400 | 5,880 | 70 | 2,016 | 24 |
| *M.R.* | 188509 | 32 | f | 8,800 | 5,280 | 60 | 2,552 | 29 |
| *W.S.* | 330194 | 32 | f | 9,200 | 5,060 | 55 | 3,964 | 42 |
| *M.K.* | 209947 | 45 | f | 6,240 | 2,558 | 41 | 2,309 | 37 |
| *S.G.* | 385496 | 46 | f | 10,400 | 5,096 | 49 | 4,680 | 45 |
| *H.H.* | 53949 | 47 | f | 5,500 | 2,585 | 47 | 1,650 | 30 |
| *E.M.* | 470364 | 49 | f | 8,700 | 5,220 | 60 | 3,132 | 36 |
| *E.L.* | 316708 | 53 | f | 11,000 | 6,270 | 57 | 3,410 | 31 |
| *M.N.* | 318043 | 58 | f | 7,900 | 4,108 | 52 | 2,528 | 32 |
| *R.D.* | 485460 | 60 | f | 8,300 | 5,478 | 66 | 2,241 | 27 |
| *I.T.* | 228111 | 69 | f | 7,000 | 4,410 | 63 | 1,750 | 25 |
| Average of women | | | | 8,385 | 4,766 | 56.4 | 2,803 | 32.9 |
| *E.H.* | 258599 | 33 | m | 5,100 | 2,652 | 52 | 2,295 | 45 |
| *H.K.* | 479500 | 35 | m | 4,700 | 2,256 | 48 | 1,645 | 35 |
| *A.J.* | 366564 | 38 | m | 5,600 | 2,128 | 38 | 2,800 | 50 |
| *K.P.* | 369416 | 43 | m | 10,800 | 7,560 | 70 | 3,024 | 28 |
| *C.E.* | 485500 | 45 | m | 9,000 | 4,590 | 51 | 3,870 | 43 |
| *A.A.* | 487800 | 45 | m | 5,500 | 3,135 | 57 | 2,090 | 38 |
| *A.K.* | 335557 | 55 | m | 9,400 | 3,760 | 40 | 4,512 | 48 |
| *R.W.* | 153528 | 56 | m | 10,900 | 4,796 | 44 | 5,014 | 46 |
| Average of men | | | | 7,625 | 3,860 | 50.0 | 3,156 | 41.6 |
| Average of men and women | | | | 8,006 | 4,403 | 53.8 | 2,944 | 36.4 |
| **Normal Subjects** | | | | | | | | |
| Ordway and Gorham (8) | | | | 5,000 to 10,000 | 3,000 to 7,000 | 60 to 70 | 1,250 to 3,500 | 25 to 35 |

TABLE 2. THE LEUKOCYTE LEVELS IN PANHYPOPITUITARISM

| Patient | Unit number | Age | Sex | Total leukocytes per cu. mm. | Neutrophiles | | Lymphocytes | |
|---|---|---|---|---|---|---|---|---|
| | | | | | number per cu. mm. | per cent | number per cu. mm. | per cent |
| *C.DeI.* | 48333 | 11 | f | 6,300 | 2,835 | 45 | 3,087 | 49 |
| *J.C.* | 189660 | 20 | f | 8,350 | 4,259 | 51 | 2,923 | 35 |
| *M.R.* | 196847 | 24 | f | 7,750 | 4,883 | 63 | 2,480 | 32 |
| *M.W.* | 160451 | 29 | f | 4,900 | 2,303 | 47 | 2,058 | 42 |
| *H.S.* | 177833 | 30 | f | 8,600 | 5,418 | 63 | 1,892 | 22 |
| *M.F.* | 161558 | 39 | f | 6,950 | 2,780 | 40 | 3,267 | 47 |
| *S.L.* | 122391 | 41 | f | 6,500 | 2,925 | 45 | 3,315 | 51 |
| *G.B.* | 187779 | 45 | f | 5,300 | 3,657 | 69 | 1,325 | 25 |
| Average of women | | | | 6,831 | 3,657 | 52.9 | 2,543 | 37.9 |
| *T.O'R.* | 83970 | 12 | m | 9,850 | 4,925 | 50 | 4,039 | 41 |
| *E.G.* | 304948 | 15 | m | 7,700 | 4,004 | 52 | 2,926 | 38 |
| *D.A.* | 199523 | 17 | m | 8,000 | 3,120 | 39 | 3,680 | 46 |
| *L.S.* | 354709 | 19 | m | 6,000 | 4,200 | 70 | 1,260 | 21 |
| *G.L.* | 306834 | 21 | m | 10,700 | 5,671 | 53 | 4,494 | 42 |
| *S.L.* | 427035 | 28 | m | 8,000 | 3,600 | 45 | 3,680 | 46 |
| *G.K.* | 171952 | 44 | m | 7,100 | 2,840 | 40 | 3,763 | 53 |
| *D.T.* | 414348 | 44 | m | 5,500 | 2,805 | 51 | 2,530 | 46 |
| *J.S.* | 396128 | 46 | m | 7,400 | 3,256 | 44 | 3,182 | 43 |
| *H.O.* | 353044 | 48 | m | 8,000 | 5,440 | 68 | 2,080 | 26 |
| *G.St.P.* | 329966 | 52 | m | 7,900 | 3,950 | 50 | 3,397 | 43 |
| *W.McC.* | 122676 | 56 | m | 6,100 | 2,745 | 45 | 3,050 | 50 |
| Average of men | | | | 7,687 | 3,880 | 50.6 | 3,173 | 41.3 |
| Average of men and women | | | | 7,345 | 3,781 | 51.5 | 2,921 | 39.9 |

techniques were employed. The absolute values for neutrophiles and lymphocytes were calculated from the percentages obtained from counting 100 leukocytes.

## RESULTS

The results are given in Tables 1 and 2, and in Figure 1. The total leukocyte, the absolute neutrophile, and the absolute lymphocyte counts averaged 11,365, 9,299, and 1,500, respectively, in the ten women with Cushing's syndrome; 8,006, 4,403, and 2,944, respectively, in the 12 women and eight men with Addison's disease; and 7,345, 3,781, and 2,921, respectively, in the eight women and 12 men with panhypopituitarism. The percentage of neutrophiles and the percentage of lymphocytes aver-

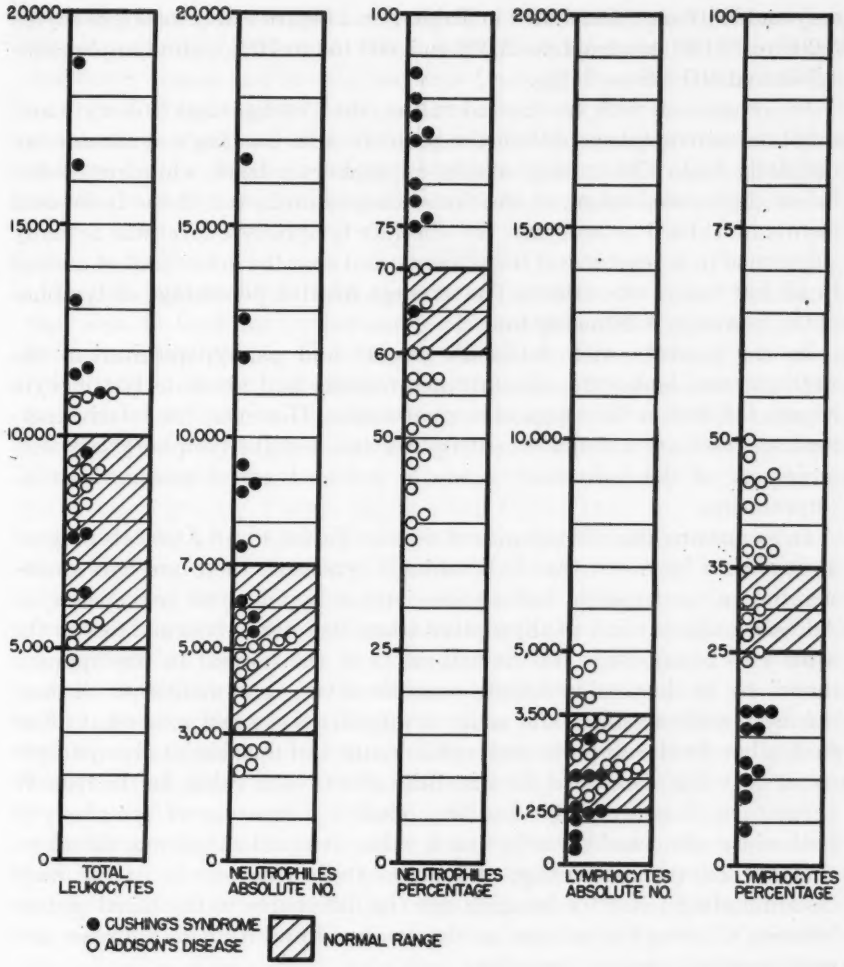


FIG. 1. Comparison of the leukocyte levels in Cushing's syndrome and in Addison's disease.

aged 81.6 and 13.1, respectively, for the Cushing's syndrome patients; 53.8 and 36.4, respectively, for the Addison's disease patients; and 51.5 and 39.9, respectively, for the panhypopituitarism patients. Men with Addison's disease or panhypopituitarism tended to have slightly lower total leukocyte and neutrophile counts, and slightly higher lymphocyte counts than women with these conditions, and thus offered slightly greater contrasts to the women with Cushing's syndrome. The normal levels of Ord-

way and Gorham (8) included in Table 1 and Figure 1 are: total leukocytes 5,000 to 10,000; neutrophiles 3,000 to 7,000 (60 to 70%); and lymphocytes 1,250 to 3,500 (25 to 35%).

In comparison with the normal values, the average total leukocyte and absolute neutrophile counts in the patients with Cushing's syndrome are definitely high. The average absolute lymphocyte level, while low, is not below the normal range; at the same time, examination of the individual counts in Table 1 reveals that the absolute lymphocyte level was actually subnormal in at least five of the patients, and near the lower limit of normal in all but one of the others. The average relative percentage of lymphocytes, however, is definitely low.

In the patients with Addison's disease and panhypopituitarism the average total leukocyte, absolute neutrophile, and absolute lymphocyte counts fall within the range of normal values. However, the relative percentages indicate a definite neutropenia and a slight lymphocytosis. Examination of the individual counts in Tables 1 and 2 sustains this interpretation.

In evaluating the five columns of data in Tables 1 and 2 (see also Figure 1) it should be noted that in Cushing's syndrome there are two abnormalities: a neutrophilic leukocytosis and a lymphocytic leukopenia; in Addison's disease and panhypopituitarism there are abnormalities in the same two components but deviations from the normal in the opposite directions. In the total leukocyte count these two abnormalities in all three disease conditions affect the value in opposite ways and somewhat offset each other. In the absolute neutrophile count and the absolute lymphocyte count only one of the two abnormalities affects each value. In the relative percentage of neutrophiles and the relative percentage of lymphocytes both of the abnormalities affect each value. It is not surprising, therefore, that the relative percentage of lymphocytes turns out to be the most discriminating value for bringing out the differences in the blood picture between Cushing's syndrome on the one hand and Addison's disease and panhypopituitarism on the other.

Thus, it has been shown that the composition of the blood leukocyte pattern, as indicated by average values, deviates from the normal in Cushing's syndrome and in Addison's disease. This impression is strengthened by an examination of the range of the absolute numbers and percentages of both neutrophiles and lymphocytes in the individual cases. The values in Figure 1 are seen to separate into two distinct groups that correlate very well with the two diagnoses, Cushing's syndrome and Addison's disease: the absolute number of neutrophiles was 6,000 or below in 18 patients with Addison's disease and in only two with Cushing's syndrome; the percentage of neutrophiles was 70 or below in all 20 patients

with Addison's disease and in only one with Cushing's syndrome; the absolute number of lymphocytes was 2,075 or above in 16 patients with Addison's disease and in only one with Cushing's syndrome; and the percentage of lymphocytes was 20 or above in all 20 patients with Addison's disease and in not one of the ten patients with Cushing's syndrome. Thus, the two groups of values overlap very little. The results in panhypopituitarism (Table 2) are almost identical with those in Addison's disease.

## DISCUSSION

Hyperadrenocorticism-with-respect-to-the-"sugar-hormone" similar to that seen in Cushing's syndrome is also a feature of the pattern of the reaction of the body to all damaging stimuli, the Adaptation Syndrome of Selye (10). A neutrophilic leukocytosis and a lymphopenia (such as have been found in Cushing's syndrome) are recognized as early hematological manifestations of such damaging events as infections, intoxications, acute blood loss, pregnancy, operations, burns, exposure to cold, and anaphylactic shock [Selye (10), Clough (2), and Van Duyn (11)].

Patients with Addison's disease or panhypopituitarism are notorious for their intolerance to infection. White and Dougherty (12) have recently demonstrated that the lymphocytes of lymphoid tissue are a storehouse for a portion of the globulin fraction of the serum (the immune globulin), and that release of this protein is under the control of the pituitary adrenocorticotrophic hormone which exerts its influence by way of the adrenal cortex. Since patients with Addison's disease or panhypopituitarism lack the adrenal cortical hormone necessary to release the immune globulin from the lymphocytes, they would tend to have too little circulating globulin and hence would not be able effectively to combat infection.

Patients with Cushing's syndrome, on the other hand, are also susceptible to infections, especially of the skin. At first thought this seems inconsistent, since in respect to the "sugar hormone" Cushing's syndrome is the opposite of Addison's disease. The explanation, however, is probably the following. The normal individual with an infection secretes "sugar hormone" which breaks down lymphoid tissue and releases immune globulin; the patient with Addison's disease or panhypopituitarism has no "sugar hormone" to release; the patient with Cushing's syndrome is releasing "sugar hormone" all of the time so that there is no store of lymphoid tissue to break down in time of stress.

The occurrence of a lymphocytosis in Addison's disease has been observed by a number of investigators since the original observations of Neusser (7). Observations have been made also by others on the neutropenia in Addison's disease [Guttman (6)]. However, the present communication, to the authors' knowledge, is the first to call attention to the ab-

solute and relative increase in neutrophiles, and particularly to the marked relative (and usually absolute) lymphopenia in Cushing's syndrome. This latter alteration may be of considerable corroborative diagnostic importance, since the lymphocytes are very resistant to toxic agents [Drinker (4)] and are rarely found to be decreased. Persistent lymphopenia should suggest Cushing's syndrome.

## SUMMARY AND CONCLUSIONS

1. The total leukocyte, the neutrophile and the lymphocyte levels in the blood of ten women with Cushing's syndrome, of 12 women and eight men with Addison's disease, and of eight women and 12 men with panhypopituitarism have been compared with each other and with the normal values.

2. Patients with Cushing's syndrome exhibit an increase in total leukocytes, an absolute and relative increase in neutrophiles, and a relative (and usually an absolute) decrease in lymphocytes in comparison with the normal levels.

3. Patients with Addison's disease or panhypopituitarism exhibit a relative neutropenia and a relative lymphocytosis in comparison with the normal levels.

4. The deviation from the normal in the percentage of lymphocytes in Cushing's syndrome is the antithesis of that in Addison's disease or in panhypopituitarism. Since it is clear from the work of others that the "sugar hormone" of the adrenal cortex depletes lymphoid tissue and the number of circulating lymphocytes, the evidence in this communication supports the hypothesis that Cushing's syndrome is an hyperadrenocorticism-with-respect-to-the-"sugar-hormone".

5. It is pointed out that the hematological manifestations of Cushing's syndrome are quite similar to those of the initial reaction of the body to non-specific damaging events [the "Adaptation Syndrome" of Selye (10)]. Since these hematological changes are due to changes in hormone production, the data herein presented strengthen the contention that the hormone alterations of Cushing's syndrome are similar to those of the early phases of the "Adaptation Syndrome".

6. It is suggested that increased sensitivity to infection in Addison's disease and in panhypopituitarism is due to lack of "sugar hormone" with which to release immune globulin from lymphoid tissue; and that increased sensitivity to infection in Cushing's syndrome is due to depletion of lymphoid tissue (from which immune globulin is normally released) because of the persistently high "sugar hormone" production.

7. A persistent lymphopenia should be sought as corroborative evidence in the diagnosis of Cushing's syndrome.

## ACKNOWLEDGEMENTS

The authors are grateful for the suggestions of Dr. James H. Means and Dr. Wyman Richardson of Boston, Mass., and of Dr. Edwin J. Kepler of Rochester, Minn.

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# ANTIDIURETIC ACTIVITY IN THE BLOOD OF NON-PREGNANT WOMEN AND WOMEN DURING NORMAL AND TOXEMIC PREGNANCY

VERA I. KRIEGER, D.Sc., AND T. B. KILVINGTON, M.Sc.

*From the Pathology Department, Women's Hospital, Melbourne, and the Physiology Department, University of Melbourne*

MUCH controversial work has been published on the relation of the antidiuretic hormone secreted by the posterior lobe of the pituitary gland to the causation of eclampsia, since the detection of this substance in the blood by Anselmino, Hoffmann and Kennedy (1) in 1932. The early work on the subject was confined solely to investigation of this antidiuretic substance in the blood, but most of the publications which appeared after the year 1937 have dealt with examination of the urine.

Various workers (1, 4, 6, 8, 11) used ultrafiltrates obtained by passing the acidified plasma through special collodion membranes. The method described by Melville (9) was just as cumbersome, but in 1941 Prendergrass, Hodes and Griffiths (10) greatly simplified the procedure by using an intraperitoneal injection of untreated serum obtained by the centrifugation of clotted blood.

Different animals were used by these workers for their biological assays of the antidiuretic hormone preparations from blood. Anselmino *et al.* (1) used rabbits, but Theobald (11) found them unsatisfactory and substituted bladder fistula dogs. These animals were also used by Melville (9) and by Byrom and Wilson (4). Prendergrass and co-workers preferred the method elaborated by Burn (3), who used a group of male rats for each assay.

Anselmino *et al.* (1) claimed to have detected antidiuretic hormone in the blood of patients suffering from eclampsia and severe toxic albuminuria of pregnancy. Hurwitz and Bullock (6) in an examination of the blood of eight women with severe toxemia of pregnancy and three hypertensive and chronic nephritic patients, failed to detect the hormone in the blood. Byrom and and Wilson (4) obtained similar results in their investigation of ten cases of pre-eclamptic toxemia and three cases of eclampsia with oedema. This was also the experience of Blazso and Dubrauszky (9) in their assays of blood from eight women with late toxemia of pregnancy. Theobald (11) however, supported Anselmino's claim by detecting antidiuretic substance in ultrafiltrates from the blood of two eclamptic patients, but disagreed with the suggestion that it was of pituitary origin. Melville (9) found the varying results of assays of blood from pregnant

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women very confusing and detected a substance with antidiuretic properties also in blood from two males and from some non-pregnant women. Prendergrass *et al.* (10) though not primarily concerned with toxemias of pregnancy found that antidiuretic substance occurred in the blood of patients with hypertension of various kinds. Two thirds of their patients who received irradiation of the hypophysis benefited by this treatment and subsequently showed absence of the factor from the blood.

Gilman and Goodman (5) demonstrated that antidiuretic hormone can be detected in the urine when a necessity for water retention is created in rats by withholding water for periods up to 96 hours or by giving excess sodium chloride. After this publication the earlier cumbersome methods for investigation of the blood were replaced by examination of the urine.

In 1940 (7) we published results of a study of urine from non-pregnant patients, from normal pregnant women and from women suffering from toxic albuminuria and eclampsia. In this investigation we used the method of Burn (3) with certain modifications such as dialysis through a cellophane bag instead of the collodion membrane. We also drew attention to fallacies in the previously employed method of estimating antidiuretic activity, in which such activity was measured by differences in the time taken to secrete half the water ingested by a set of four rats given water by mouth and an injection of the urine preparation being investigated, and a control set of four rats which was given water only. We therefore assessed antidiuretic effects by measuring area differences subtended by graphs obtained when the total volumes of urine excreted by control rats and by treated rats over a period of five hours, are plotted against the time. In addition the control set were injected with a corresponding volume of physiological saline to equalize all conditions in both sets of rats.

Statistical analysis of our results at that time showed that small amounts of a substance with the power of inhibiting water diuresis was present in the urine of some non-pregnant women, more often in that of normal pregnant women, and frequently and in much greater concentration in the urine of women with pre-eclampsia and eclampsia.

Throughout the investigation 100 cc. samples of urine from the patients being tested were assayed. Area differences were obtained by plotting time against the total volume of urine excreted in five hours by groups of four male rats; the units of abscissa and ordinate were 60 minutes per inch and 10 cc. per inch respectively. The ranges of values for the different groups were as follows:

| | |
|---|---|
| Non-pregnant women | 0.16–1.73 sq. in. |
| Normal pregnant women | 1.83–3.45 sq. in. |
| Toxemic women | 1.93–5.45 sq. in. |
| Eclamptic women | 5.17–8.70 sq. in. |

During these and further investigations we noted relatively large variations in the urinary secretion of different sets of control rats. It was therefore obvious that it was necessary to determine the magnitude of the area differences which actually represented an antidiuretic effect. From the statistic analysis of two hundred and fifty eight experiments it was found that an area difference of 5.6. sq. in. was the minimum value representing a true antidiuretic effect. Consequently our previous conclusions must be modified. We are now of the opinion that although there is a significant difference in areas shown in the test of the various groups of women mentioned above, true antidiuretic effects were obtained only in the group of eclamptic women. Even in this group a few area differences were not significant, but the majority demonstrated the presence of antidiuretic activity. Evidence is, however, accumulating in at present uncompleted studies, which may lead to a different interpretation of these and other workers' results.

Difficulties which have arisen in these investigations have led us to direct attention temporarily to blood analyses, using the simple method introduced by Prendergrass *et al.* (10) and the results are as follows:—In all, blood from 303 women was examined, the patients including non-pregnant women, women during normal pregnancy, and women with eclampsia. In the normally pregnant the tests were made (a) during early months, (b) between the seven and one half and eight and one half months of pregnancy, and (c) at term.

The results of the investigation are summarized in Table 1.

TABLE 1. ANTIDIURETIC HORMONE IN BLOOD

| Type of patient | No. of patients investigated | % of patients with antidiuretic substance in the blood |
|---|---|---|
| Non-pregnant women | 45 | 20 |
| *Normal pregnancy* | | |
| (a) Early | 43 | — |
| (b) 7½–8½ months | 39 | 8 |
| (c) At parturition | 41 | 41 |
| (d) Puerperium | 97 | 37 |
| Eclampsia | 38 | 29 |

It is interesting to note that whilst there is evidence of antidiuretic activity in the blood of some (20 per cent) of the non-pregnant women, no activity was found in the blood of any of the patients examined during the

early months of pregnancy and only in eight per cent of those tested in the period between the thirtieth and the thirty-eighth weeks of pregnancy. At term, on the other hand, antidiuretic activity was present in the blood of 41 per cent of the patients and was also found in the blood of 37 per cent of those tested in the period three to eight days post-partum. The blood of 29 per cent of a group of women with eclampsia or severe pre-eclampsia also exhibited antidiuretic properties. If these patients were divided into two groups according to whether the blood was investigated in the antepartum period or intra and post-partum, no antidiuretic activity was observed in the first group. In the second group however, there was a similar proportion of effective and non-effective samples to that in normal pregnant patients at parturition.

These results, although based on comparatively small figures, suggest that the occurrence of antidiuretic substance in the blood may be a normal physiological process associated with labor and the puerperium. They do not support the assertion of Anselmino and others that antidiuretic hormone is a factor in the causation of eclampsia.

They also offer an explanation for the contradictory findings reported in the literature. As most of these latter conclusions are based on exceedingly small numbers of cases it is quite possible that the divergent results are mainly due to the relation between the time when the blood sample was taken and the onset of labor.

## SUMMARY

1. Previous methods and results of assay of antidiuretic hormone in the blood have been briefly reviewed.
2. The interpretation of the results of antidiuretic hormone in urine which we published in 1940, has been modified in the light of the results of statistical treatment of control experiments.
3. Three hundred and three assays of antidiuretic activity in the blood of non-pregnant women and of women with normal and abnormal pregnancy are reported.
4. Our findings do not support the claim that antidiuretic hormone is a factor in the causation of eclampsia.

## ACKNOWLEDGEMENTS

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# *Abstracts of*
# CURRENT ENDOCRINE LITERATURE

*Editor:* D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, I. BRAM, F. A. DE LA BALZE, ANNE P. FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MACARTHUR, T. H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZO-MEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH AND L. T. SAMUELS.

## ADRENALS

BUTCHER, E. O. Effects of adrenalectomy on pigmentation of hair in rats fed a deficient diet. *Proc. Soc. Exper. Biol. & Med. 60* (3): 396–397 (1945).

Black hooded rats of the Long-Evans strain were fed a vitamin B-complex free diet, supplemented with thiamine, riboflavin and pyridoxine. Graying of the hair resulted in rats fed this diet. New hair produced following complete adrenalectomy in rats maintained on the B-complex deficient diet was well pigmented. In twenty 22-day old rats the adrenals were transplanted into the kidneys and sparse dull gray hair appeared between the ages of 45 and 60 days. Microscopic examination showed that the cortical material of the adrenal transplants persisted and that the medullary portion was absent. It was concluded that the lack of the cortex was related to the increased pigmentation which followed adrenalectomy.—*F.N.A.*

HOUSSAY, B. A. The influence of adrenal insufficiency during pregnancy on the mother and on the offspring. *Rev. Soc. argent. de biol. 21:* 316 (1945).

Fifty per cent of rats adrenalectomized during pregnancy died before parturition if no sodium chloride was administered in the drinking water. If one per cent sodium chloride solution was given as drinking water, only one seventh of the pregnant animals died, a mortality equal to that in the control animals; therefore, sodium chloride had a definite protective action. In the second and third pregnancies following adrenalectomy, the mortality was the same as in the control animals even when no extra salt was given; this was due to the fact that the accessory adrenal tissue had had time to hypertrophy. The offspring of the first litter after adrenalectomy were significantly smaller than normal, but in the subsequent litters the offspring became increasingly heavier as the accessory adrenals hypertrophied. The numbers in each litter were normal. Rats littering 10 to 15 days after adrenalectomy usually had scarcity and sometimes complete absence of milk; the offspring died after a few days or did not grow normally. Growth was normal only in those born 25 to 50 days or more after adrenalectomy. The average weight of the adrenals of the newly-born from adrenalectomized rats was greater than normal, but the difference was not significant in all litters. The adrenal weight per gram of body weight was nearly always significantly larger than in the controls. Injection of adrenotrophin into pregnant rats caused hypertrophy of their adrenals, but not of those of their offspring; parturition did not occur or was incomplete and the fetuses died. Desoxycorti-

costerone injected into pregnant rats prolonged parturition, with subsequent excessive growth of the fetuses and difficulty in parturition; the offsprings' adrenals were not atrophied.—*J.R.R.-M.*

MALENCHINI, M., E. B. DEL CASTILLO, AND J. ROCA. Radiologic exploration of the suprarenal gland. *Prensa méd. argent. 32:* 739 (1945).

The authors have infiltrated air into the region of the kidney and have obtained radiographic images which permit visualization of the suprarenal glands. The aerograms present no difficulty in interpretation: the gland appears as an easily recognizable image in its normal as well as in its tumoral state. The method was employed in 60 cases with a minimum of difficulty. Subsequently, these patients were carefully examined, and none presented manifestations of suprarenal insufficiency. The authors believe that there is no reason to explore the glands surgically without first having explored the glands bilaterally by the air injection technique. They suggest that the application of the method can be improved if radioscopy is employed before radiography.—*F.A.de laB.*

PINTO, R. M. Direct and indirect action of estrogens on the suprarenal glands. *Rev. Soc. argent. de biol. 21:* 136 (1945).

The author studied white adult female rats. As evidence for a direct action of estrogens on the suprarenal gland he reports that: (1) The injection of estrogens to castrated and hypophysectomized animals does not prevent or modify the adrenal atrophy caused by the hypophysectomy. (2) If castrated and hypophysectomized rats are treated with extracts of the anterior lobe of the hypophysis, the injection of estrogens prevents further loss of weight of the adrenals and maintains the three layers of the adrenal cortex. As evidence for an indirect action of estrogens through the hypophysis on the suprarenal gland he reports that: (1) The injection of estrogens to normal female rats increases the adrenotrophic action of their hypophyses. (2) The administration of estrogens to castrated rats produces a marked hypertrophy of the adrenals.—*F.A.de laB.*

SELYE, H., ELEANOR BELAND, AND OCTAVIA SYLVESTER. Brain lesions following prolonged overdosage with desoxycorticosterone acetate. *Exper. Med. & Surg. 2:* 224 (1944).

Desoxycorticosterone acetate (D.C.A.) caused characteristic motor disturbances in a large number of rats sensitized to this hormone by unilateral nephrectomy and a high salt intake. These motor disturbances are essentially different in their clinical characteristics from the general anesthesia and the periodic familial paralysis-like symptoms which can be elicited by the same hormone under different experimental conditions. The motor disturbances described in this communication proved to be accompanied by—and probably due to—periarteritis nodosa of the cerebral vessels. The morphologic characteristics of these vascular lesions as well as the resulting brain hemorrhages and edema have been described. Using the pellet implantation technic, it could be shown that in sensitized rats, less than 1 mg. of D.C.A. per day suffices to produce severe periarteritis nodosa and malignant nephrosclerosis.—*Author's Abstract.*

## ENDOCRINE GENERAL

ALVAREZ, W. C. Stoppage of bodily growth in a boy with stenosing enteritis. *Gastroenterology 5:* 281 (1945).

This is the story of a 17 year old boy who began to suffer crampy abdominal pains at the age of 13. Throughout his illness of four years, there had been acute episodes of fever, stasis vomiting and crampy abdominal pain, but at no time any frank symptoms of intestinal obstruction. At the time of his examination his weight was 95 lbs. (at the age of 13 his weight was 120 lbs.). His voice was high pitched, his pubic hair was normal, but no prostate gland could be made out. His basal metabolic rate was minus 12. X-ray of the small bowel revealed an ulcerative hyperplastic enteritis involving the upper part of the jejunum and causing partial obstruction. Following operation he developed into a normal, broad-shouldered adult, but suffered from a severe ulcerative colitis.—*T.H.McG.*

ABARBANEL, A. R. AND J. H. LEATHEM. Studies in amenorrhea, oligomenorrhea, and anovulomenorrhea 1. Effect of equine gonadotropin upon establishment of cyclic menses and ovulation. *Am. J. Obst. & Gynec. 50* (3): 262–269 (1945).

The authors studied the effects of equine gonadotropin in 22 women who had varying degrees of ovarian failure. Three had nonoccurrence of menarche, 11 had no bleeding for from four to 26 months, eight had relatively infrequent uterine bleeding and one had cyclic anovulatory bleeding. Equine gonadotropin was usually given every two to three days for four doses. The total dosage varied from 400 International Units to 6,800 International Units. Both intramuscular and intravenous routes were used. As a rule, seven to twenty-one days after the last injection of equine gonadotropin, an endometrial biopsy was made. The three patients with delayed menarche failed to bleed. Of the 11 patients with intercurrent amenorrhea, ovulation was apparently stimulated in two but only one continued to have regular menses. In the seven patients with infrequent bleeding, one had restored cyclic menses but no ovulatory response. In the one instance of anovulatory bleeding, equine gonadotropin was ineffectual. The authors state that nine of these 22 patients were later "salvaged" with an adequate diet and, usually, thyroid extract.—*C.D.D.*

BOWMAN, D. C. Reducing properties of the chorionic gonadotropic hormone as related to the chemical determination of pregnancy. *Am. J. Obst. & Gynec. 50* (2): 218–220 (1945).

The author presents various considerations and data that point out that at present a suitable means for the chemical determination of pregnancy based upon the reducing properties of gonadotropin, if feasible at all, has not as yet been adequately defined.—*C.D.D.*

CLARK, G. AND H. G. BIRCH. Hormonal modifications of social behavior. I. The effect of sex-hormone administration on the social status of a male castrate chimpanzee. *Psychosom. Med. 7:* 321 (1945).

The effects of male and female sex-hormone administration on the dominance status of a male castrate were studied in a food-competition situation. The animal with which the castrate was paired was an intact male of approximately the same size and age as the treated subject. The results showed: that the dominance status of the castrate was enhanced by male sex hormone therapy; that the castrate assumed subordinate status as a result of the administration of female sex hormone; that well-established habits of social response were acquired by the animals and tended to persist after cessation of

hormone administration; that the persistent habits of response could be modified and eventually reversed by appropriate hormone treatment. The results are discussed in connection with the general problem of social dominance. Several hypotheses as to the nature of the mechanism underlying the effects of sex hormone on the social interactions of the chimpanzee are considered.—*Authors' Summary.*

CEBALLOS, A., T. V. FRANK, AND W. F. SIMPSON, JR. Waterhouse-Friderichsen syndrome. A report of eight cases at the Children's Hospital, Washington, D. C. *J. Pediat. 27:* 281 (1945).

The authors have reviewed the literature on this condition since 1941, when a previous report was published from their hospital (Am. J. Med. Sci. *201:* 263, 1941). They also report eight additional cases that have been seen since that date. In this series, the average age incidence was found to be 44 months; the average temperature on admission to the hospital to be 104.6 degrees F.; and the average duration of illness in known instances to be about 15 hours. An admission diagnosis of possible Waterhouse-Friderichsen syndrome was made in six of the eight cases. In every case bilateral adrenal hemorrhage was revealed at autopsy. Laboratory findings were extremely variable; meningococci were recovered from both spinal fluid and blood in one half of the cases. The organisms were recovered in the one instance in which smears were made from the petechial areas. A table of the essential features of these eight cases is included. The authors conclude: 1) there is an increasing number of cases of this syndrome in the literature in recent years, probably due both to its more accurate recognition and to the increased incidence of meningococcic infections in the past two years; 2) the condition is believed to be the result of fulminating meningococcemia and shock, and the pathologic findings can be explained on the toxic results of the organisms; 3) present usage of the term, Waterhouse-Friderichsen syndrome should be confined to those cases exhibiting the fairly typical course as described, and undoubtedly to those patients whose symptomatology was confirmed by autopsy; 4) care should be taken in the early recognition and differentiation of this syndrome from acute meningococcemia; and 5) the present outline of treatment centers on control of the bacteremia and measures aimed to combat shock, with secondary symptomatic and supportive treatment.—*E.C.R.,Jr.*

ENGLER, M. The causation of Mongolism. *Proc. Roy. Soc. Med. 38:* 211 (1945).

The theories of the causes of Mongolism are reviewed and subdivided into 1) general exogenous factors such as exhaustion, alcoholism and syphilis, 2) increased amniotic pressure, and 3) the theory of nidation. The association of the use of abortifacients and Mongolism, and the frequency of miscarriages preceding the birth of Mongols are cited. The author reviews evidence for vitamin and hormone deficiencies as the cause of Mongolism, and feels that each can be related to endometrial abnormalities resulting from the deficiencies. He discounts alcoholism but cites the association of syphilis and Mongolism, and further relates the theory of increased amniotic pressure to faulty nidation.—*R.C.*

FRANK, R. T. The search for the female sex hormones. *Am. J. Obst. & Gynec. 50* (6): 757–760 (1945).

The author gives a brief and interesting historical account of the recognition and subsequent isolation of the female sex hormones.—*C.D.D.*

GRAHAM-BRYCE, I., A. K. BULLEN, AND W. H. FORBES. Effect of pregnenolone on the ability to perform prolonged psychomotor tests. *Psychosom. Med. 7:* 353 (1945).

Pregnenolone administered to five civilian subjects did not produce beneficial results on prolonged psychomotor tests as it had in the case of seven army pilots tested similarly by Pincus and Hoagland. A comparison of the two sets of experiments suggests that positive effects of the drug will be shown only by people who are under stress.—*Authors' Summary.*

GROSSMANN, L. L. The treatment of primary dysmenorrhea with deproteinated pancreatic extract. *Am. J. Obst. & Gynec. 50* (4): 411–416 (1945).

The author reported the use of a deproteinated pancreatic extract, a spasmolytic agent, in the treatment of 56 dysmenorrheic patients. From 1.5 to 4 cubic centimeters were given intramuscularly at the onset of symptoms. Complete relief was produced in 79.4 per cent of private patients and 53.7 per cent of an industrial group. Partial relief occurred in 17.5 per cent in the former group and 14.6 per cent of the latter.—*C.D.D.*

## PANCREAS

MILLER, H. C. Cardiac hypertrophy and extramedullary erythropoiesis in newborn infants of prediabetic mothers. *Am. J. M. Sc. 209* (4): 447–455 (1945).

Infants born to mothers with diabetes mellitus may show the following changes: macrosomia, cardiac hypertrophy, hyperplasia of the islands of Langerhans, excessive extramedullary erythropoiesis, adrenal hyperplasia and an increase in the eosinophil elements of the anterior pituitary gland. In the course of studies on such infants, it was observed that in seven infants the same changes were present before signs or symptoms of diabetes mellitus appeared in their mothers. None of the mothers had any symptoms of diabetes before or during the pregnancies under discussion; signs and symptoms of the disease developed from two days to five years following the births of these seven infants. The significant postmortem findings in the five of these seven that died are tabulated, and the case reports of the two that survived are presented. The differential diagnosis of these infants is discussed. The author stresses that the diagnosis of this syndrome in infants born to mothers who have not yet developed diabetes is of importance to the clinician not only in directing the care of the infant in the neonatal period, but in anticipating the onset of diabetes mellitus in the mother, since the birth of an infant with these findings may be the first sign of impending diabetes.—*E.C.R., Jr.*

PALMER, L. J. and R. H. BARNES. Pregnancy in the diabetic. *West. J. Surg. 53:* 195–202 (1945).

Sixty-eight pregnancies in 41 diabetic women followed at the Mason Clinic in the fourteen years prior to June 1944 are reported. Thirty-seven pregnancies treated by the authors resulted in 22 living children (60 per cent). Specific hormonal therapy (other than insulin) was not employed. The group of diabetics who developed the disease before the age of 15 displayed the least fetal survival, the highest incidence of albuminuria,

edema and hypertension and showed the greatest gain in weight. Because of the frequency, as yet unexplained, with which the death of the fetus occurs in the last four weeks of pregnancy, the authors believe that caesarian section at the thirty-sixth week will yield the highest percentage of surviving children. Although the parity of the pregnancy had no effect upon fetal survival in this series, the authors feel that more than two pregnancies exact an excessive physical sacrifice from a diabetic woman. Because of the low renal threshold in pregnancy, insulin dosage must be guided by frequent determinations of the blood sugar if hypoglycemia is to be avoided.—*J.M.*

PETERMAN, M. G. Pentosuria with diabetic symptoms. *J. Pediat. 26* (3): 296–297 (1945).

The case is reported of a Jewish male infant who: 1) had a family history of diabetes mellitus on both sides; 2) had a normal birth and development, but was slow to gain weight; 3) was indulged and fed sweets at odd times; 4) at 22 months suddenly developed polyphagia (his hunger was so intense that he would steal food and hide it around the home), polydipsia, polyuria, pollakiuria, and mellituria; 5) had sugar in the urine persistently in spite of normal fasting blood sugar levels and normal glucose tolerance curves; 6) proved to have pentosuria by fermentation and orcinol tests; 7) developed furunculosis before treatment was instituted; 8) continued to have pentosuria for two years during which he followed a low carbohydrate diet and gradually improved; and 9) ultimately lost the pentosuria and apparently recovered completely.—*E.C.R.,Jr.*

RICKETTS, H. T. AND F. J. STARE. The effect of insulin on the in vitro respiration of human skeletal muscle. *J. Lab. & Clin. Med. 30* (7): 594–599 (1945).

The effect on respiration of insulin, dicarboxylic acids (fumaric and glutamic), and co-carboxylase was observed in minced samples of muscle tissue from uncontrolled insulin-sensitive, uncontrolled insulin-insensitive, and controlled insulin-sensitive human diabetics. In all, eight diabetic subjects were studied. Insulin did not influence the uptake of oxygen by the two latter groups, nor indeed did it influence the respiration of skeletal muscle from patients without metabolic or muscular disease. On the contrary, it increased and prolonged the rate of the in vitro oxygen consumption of minced muscle from the insulin sensitive group of uncontrolled diabetics. In some instances the action could be demonsrated only after a dicarboxylic acid had been added to the medium and in one instance it was necessary to supply co-carboxylase as well.—*T.H.McG.*

SHERIDAN, E. P. Liver abscess, pneumonia and empyema due to Friedlander's bacillus in diabetes mellitus. *New England J. Med. 233* (18): 528–529 (1945).

Two cases of liver abscess are reported in patients suffering from diabetes. In one there were multiple abscesses in other tissues as well. These were the only cases among more than twenty thousand diabetic patients treated at the George F. Baker clinic. Since 25 other cases have been reported in the literature in some at least not associated with diabetes the diabetic condition does not seem to be particularly conducive to this infection. Surprise is expressed that the condition does not occur oftener.—*L.T.S.*

URBACH, E. Skin diabetes, hyperglycodermia without hyperglycemia. *J.A.M.A. 129* (6): 438–440 (1945).

The term "skin diabetes" is applied to cases of furunculosis, eczema or pruritis which show a high fasting skin sugar level with a normal blood sugar curve and a fall in the high skin sugar level together with a pronounced improvement of the dermatitis on a low carbohydrate diet, sometimes with insulin. The patients are often obese and plethoric individuals. The author describes the technique of measuring skin sugar elsewhere. He states here that the normal fasting skin sugar level is below 60 mg. per cent the average being 58 mg. per cent and it is rarely over 65.5 mg. per cent. After a glucose tolerance test the skin sugar should return to the fasting level in not more than three hours. One third of the patients reported here had skin sugars over 80 mg. per cent. A diagnosis of "independent cutaneous glychohistechia" is made if the fasting skin sugar level is over 60 mg. per cent and the skin sugar/blood sugar ratio is over 70 per cent. The latter criterion automatically excludes cases of diabetes mellitus. The relationship of the two conditions is discussed. Skin diabetes may obtain in cases of ordinary diabetes, on the other hand either disease may exist alone. Although the etiology may be different, the treatment is the same.—*A.P.F.*

WHITE, P. Pregnancy complicating diabetes. *J.A.M.A. 128* (3): 181–182 (1945).

A most challenging list of abnormalities common in diabetic pregnancies is given: early spontaneous abortion, 25 per cent of cases; pre-eclamptic toxemia, 36 per cent; breech presentation, 33 per cent; failure of lactation, almost 100 per cent. Low renal threshold for glucose and a tendency to water retention are also common. Eighty per cent of fetuses are oversized and most show edema, splanchnomegaly, excessive hematopoesis and jaundice. Young diabetic women often have amenorrhea, metrorrhagia and increases level of follicle-stimulating hormone. Atrophy of the ovary and poor follicle development are seen pathologically. The sex hormone imbalance which the author considers all important in producing the abnormalities of pregnancy consists in a fall of pregnandiol in the urine and a rise of chorionic gonadotropin. One hundred eighty-one cases were studied with great care. Fifty-two with normal hormone production had no abortions, only two toxemias and a 96 per cent fetal survival. Thirty-eight cases with the imbalance described showed premature delivery in 40 per cent, toxemia in 50 per cent and a fetal survival of 50 per cent. Ninety-one cases showed a similar imbalance and were treated with estrin and progesterone, usually large doses injected daily. Premature deliveries in this group were 15 per cent and fetal survival 90 per cent. Toxemia appeared to be altered or prevented.—*A.P.F.*

## PARATHYROID

MCCHESNEY, E. W. AND N. J. GIACOMINO. The treatment of experimental hypoparathyroidism in dogs. *J. Clin. Investigation 24* (5): 680–686 (1945).

Following total thyroid-parathyroidectomy, the blood calcium of each of ten mongrel dogs on a standard diet was allowed to drop to 7.5 mg. per 100 cc. of blood after which the following observations were made. Calcium gluconate in doses of one to two gm. per kg. of body weight per day in conjunction with one to two gm. of ammonium chloride daily

to prevent alkalosis sufficed to keep the animals in good condition, despite the fact that their serum calcium did not rise above 7.0 mg. per 100 cc. Parathyroid extract in doses of 100 units per kg. daily caused a maximum rise of three to four mg. per 100 cc. in serum calcium and a fall of one to three mg. in serum phosphorus. Elevated values might persist for seven days. The responses to vitamin $D_2$ and $D_3$ did not differ significantly from each other either in kind or degree. A single dose of two mg. per kg. of either resulted in a maximal rise of serum calcium to from 11.7 to 13.7 mg. per 100 cc. in from three to seven days. The duration of the responses varied from three to six weeks. In single doses of one mg. per kg. of body weight, dihydrotachysterol produced maximal elevations of the blood serum calcium (up to 14.6 mg. per 100 cc.) within three to four days, and a duration of the response for from 16 to 40 days. A radical increase in the calcium content of the diet (from 0.38 per cent to 0.92 per cent) did not alter the character or magnitude of the response which was in sharp contrast to the high blood serum calcium levels following the increased injection of calcium in conjunction with vitamin D therapy. The authors concluded that dihydrotachysterol had more than twice the calcemic effect of vitamin D in dogs, in contrast to a ratio of about six to one in man. In summary, vitamin $D_2$ and $D_3$ are similar in action and produce a calcemic effect in both the normal and the parathyroidectomized dog, but more marked in the latter. If parathyroid and vitamin D are given simultaneously to the thyroid-parathyroidectomized animal there is an additive effect with a still greater increase in blood serum calcium, rather than a regulatory effect as should be expected. This led the authors to conclude that some principle elaborated by the parathyroid which reacts positively against an elevated serum calcium is missing from the extracts made by Collip and Clark. Dihydrotachysterol evokes much the same responses in the parathyroidectomized dog as it does in the normal dog but unlike vitamin D, the magnitude of the reaction is not readily influenced by variations in the calcium content of the diet. Dihydrotachysterol probably acts by causing (1) "an increase in urinary phosphate excretion with the serum phosphorous becoming normal, (2) an increase in the absorption of calcium with higher serum calcium, and (3) no increased output of phosphate in advanced renal damage."—*T.H.McG.*

## THYROID

BISSELL, G. W. The magnesium partition in hyperthyroidism, with special reference to the effect of thiouracil. *Am. J. M. Sc. 210* (2): 195–200 (1945).

The author was not able to demonstrate a significant increase in the percentage of the non-diffusable fraction of the total serum magnesium of 24 patients with hyperthyroidism as compared to that of 18 normal persons. The average for the thyrotoxics was $30.5 \pm 1.9$ per cent, and for the normals was $30.4 \pm 1.1$ per cent. Thiouracil had no constant effect on the magnesium fractions in hyperthyroidism. Attention is called to the fact that the non-diffusable fraction ranged between 5 and 58 per cent of the total serum magnesium in the thyrotoxic patients, in contrast to a range from 17 to 42 per cent in the normal individuals. The author concludes that the magnesium partition will have to be studied in a greater number of metabolic disturbances before its significance in hyperthyroidism may be evaluated.—*E.C.R., Jr.*

COLE, W. H., D. P. SLAUGHTER, AND L. J. ROSSITER. Potential dangers of non-toxic nodular goitre. *J.A.M.A. 127* (14): 883–888 (1945).

This is a discussion of the advisability of removing non-toxic nodular goitre. Car-

cinoma was encountered in 7.2 per cent of the authors' 523 reported cases of nodular goitre and much more frequently in the non-toxic cases. It was twice as common in single nodules. Early cancer can usually be seen to originate in afetal adenoma but most cases have obliterated their site of origin by the time they are seen. The authors believe that some degree of toxicity eventually develops in about half the patients with nodular goitre. The incidence increases with age. The symptoms are very apt to be mild or borderline. Mechanical or obstructive symptoms occurred in about 20 per cent of the 523 cases. —*A.P.F.*

CRUZ COKE, E., G. R. MUJICA, AND H. DIAZ DE VALDES. Thiourea and thiouracil in hyperthyroidism. *Rev. méd. de Chile 73:* 223 (1945).

The use of thiourea and thiouracil was begun in Chile early in 1943, simultaneously with its introduction by North American workers. Fifty-two patients have been treated, 29 exclusively with thiourea, 18 with thiouracil and five with a combination of the two drugs. The initial dose of thiourea was 0.6 gm., of thiouracil 0.5 gm. while if good tolerance was shown the dose was raised gradually to a maximum of 1.80 gm. Thiouracil was the better tolerated. The most important sign of intolerance was gastralgia. A slight leucocytosis occurred in some, but none showed leucopenia, neutropenia, nor thrombocytopenia as an exclusive effect of the drug. The drug alone was used to effect a cure in all cases of hyperthyroidism without tumor, also in Basedow's syndrome and toxic tumors, in which the volume of the gland was relatively small. In diffuse toxic tumors or in nodular tumors of great size, the use of the drug was a preoperative procedure. Of all cases, satisfactory results were obtained in 84.6 per cent. In 11.5 per cent the drug was used preoperatively and in 3.8 per cent it was not successful. Subjective symptomatology began to improve within two to four weeks.—*Courtesy Biol. Absts.*

GARGILL, S. L. AND M. F. LESSES. Toxic reaction to thiouracil. *J.A.M.A. 127* (14): 890–898 (1945).

Toxic reactions in eight of 43 patients treated with thiouracil are described in detail. They included one fatal and one non-fatal case of agranulocytosis, one non-fatal case of granulocytopenia, two cases of jaundice, two cases of drug fever and two cases of submaxillary salivary gland swelling. The incidence of agranulocytosis appeared to bear no relation to the amount, duration or continuity of treatment. Some of the other patients were continued on thiouracil in reduced doses. The cases of jaundice were interesting in that liver biopsy taken at operation in one showed bile stasis with normal liver parenchyma, while the other also showed obstructive jaundice clinically. The dangers of thiouracil are emphasized.—*A.P.F.*

HAINES, S. F. AND F. R. KEATING. Unusual reactions following the use of thiouracil. *Proc. Central Soc. Clin. Res. 17:* 11 (1944).

In two instances of severe recurrent exophthalmic goiter the gland was not palpably enlarged but symptoms of hyperthyroidism were severe and the BMR was greatly elevated. In each case the administration of thiouracil was followed after several days by diminution of the signs and symptoms of hyperthyroidism and by lowering of the BMR. Transient painful swellings of subcutaneous tissues occurred; at the same time the value for the plasma chloride was increased and the $CO_2$-combining power of the plasma was decreased. In one case, myoclonic contractions of various muscles, more particularly of the facial muscles, occurred, and at the same time severe somnolence and confusion were present. The twitchings persisted for several days after the treatment

was stopped. Subsequent administration of the drug on two separate occasions was followed rapidly by a resumption of the untoward symptoms and signs. In the other case, a similar state of somnolence and mental confusion occurred during a second period of administration of the drug. These reactions probably are dependent upon a toxic disturbance of the central nervous system.—*Courtesy Biol. Absts.*

HIGGINS, G. M. A study of the goitrogen, promizole, with reference to the thyroid, metabolism and the blood. *Am. J. M. Sc. 210* (3): 347–352 (1945).

The administration of promizole (4,2′-diaminophenyl-5′-thiazolyl sulfone) to a series of immature and adult rats resulted in the following conclusions: 1) changes proportional to the daily amount of promizole and resembling those produced by thiourea-like and certain sulfonamide compounds were produced in the thyroid glands; these changes included extreme increases in cell heights, complete loss of colloid and extreme hyperplasia with the formation of new acini in the walls of pre-existing acini, and large increases in thyroid gland weights; 2) slight, but real, increases in pituitary gland weights not correlated with increases in thyroid gland weights were observed; it was felt that further proof was needed to establish that the increases in pituitary weights were due to hyperplasia of the basophilic cells or to an increase in the thyrotropic hormone content of the pituitary; 3) a decrease in the basal metabolic rate proportional to the degree of hyperplasia and to the loss of colloid from the thyroid acini occurred in most animals made goitrous by promizole; 4) withdrawal of the drug resulted in recovery of the normal thyroid patterns and an elevation of the metabolic rates; however, the rate of recovery was not as rapid as that from certain other goitrogens since normal colloid patterns still were not restored four weeks after removal of the drug; 5) promizole interfered with the utilization of iodine by the thyroid and thus prevented the synthesis of thyroxin, since thyroxin and thyroid extract but not iodine inhibited the effects of promizole; 6) anemia, with lowered numbers of erythrocytes and concentrations of hemoglobin, was induced as an untoward effect in young but not in adult rats; 7) leukopenia and granulocytopenia were not induced by the amounts of drug administered; and 8) the drug induced considerable alopecia in growing animals (but not in adult animals) fed a purified diet; it could be largely prevented by a dietary factor.—*E. C. R., Jr.*

HURXTHAL, L. M. AND NATALIJA MUSULIN. Hypertrichosis and myxedema. *Lahey Clin. Bull. 4:* 102–109 (1945).

A case of myxedema is reported in which excess hair growth occurred and then disappeared after thyroid therapy. Among the possible theoretical explanations of the unusual phenomenology is that the cause of the myxedema was primary deficiency of thyroid secretion and that a compensatory over-activity of the anterior pituitary occurred. This might have given rise to over-production of adrenocorticotropin with resulting excessive activity of the adrenal cortex and hence of hirsuitism.—*R.G.H.*

KING, B. T. AND L. J. ROSELLINI. Treatment of acute thyroiditis with thiouracil. *J.A.M.A. 129* (4): 267–268 (1945).

Ten cases of acute thyroiditis, three of them of the migratory type, and one case of struma lymphomatosa (Hashimoto's struma), were treated with thiouracil. In eight of the cases where symptoms were of less than three weeks' duration, local and systemic

symptoms as well as enlargement of the gland disappeared completely in a week. One patient who could not tolerate the drug, one case of five months' duration and the patient with Hashimoto's struma were not helped. The authors describe the disease as an acute inflammatory process in the thyroid associated with fever, leucocytosis, malaise and often slight hyperthyroidism, which usually lasts from six weeks to six months. In their previous experience, x-ray was sometimes beneficial and sometimes detrimental while all the other treatments tried were useless. Thiouracil appeared to be a highly effective specific for early cases.—*A.P.F.*

McGAVACK, T. H. AND I. J. DREKTER. The behavior of blood cholesterol in thyrotoxic patients under treatment with thiouracil. *J. Lab. & Clin. Med. 30* (7): 586–589 (1945).

Cholesterol esters of the blood varied directly with the total figure and in all observations constituted a normal percentage thereof. Of 52 thyrotoxic patients in whom the fasting total cholesterol was determined, eleven showed an abnormally high value (greater than 200 mg. per 100 cc. of blood) before treatment with thiouracil. At the same time their averaged basal metabolic rate was plus 48.5 per cent. In the serial examination of 36 patients under treatment, the decrease in basal metabolic rate and cholesterol roughly paralleled each other. The actual values varied widely from patient to patient, but the trend was constant for each patient. Higher than normal values usually appeared when the basal metabolic rate lay between plus five and plus 15 per cent. Clinically, the patients felt their best with high normal values for cholesterol and a metabolism lying within the range of figures just quoted.—*T.H.McG.*

PERKIN, H. J. An "iodase" in the blood of patients with clinical hyperthyroidism. A preliminary report. *Lahey Clin. Bull. 4:* 124–126 (1945).

In about 50 cases of clinical hyperthyroidism it was found that addition of "thyroid proteose" to the patients' blood led to an augmentation of the "inorganic iodine" content whereas in normal blood the "organic iodine" is increased. The observation suggests that the blood in such hyperthyroid cases contains an enzyme, "iodase" by the action of which the thyroid proteose is broken down to a simpler form.—*R.G.H.*

RAAB, W. Diminution of epinephrine sensitivity of the normal human heart through thiouracil. *J. Lab. & Clin. Med. 30* (9): 774–779 (1945).

Thiouracil in doses of 0.4 gm. daily was fed to each of ten physically normal human subjects for a three months' period of time. Variations in the response of the pulse rate and the electrocardiogram to 0.5 and 1.0 mg. doses of epinephrine before and during treatment with thiouracil were compared. After thiouracil, the depression of the T waves produced by epinephrine alone were "diminished or entirely abolished." Similarly the acceleration in pulse rate ordinarily caused by epinephrine was abolished after the use of thiouracil. Changes in the basal metabolic rate as a result of the administration of thiouracil were slight in eight of the ten subjects. Reactions of the blood pressure to epinephrine were "uncharacteristically altered after thiouracil medication." The author concludes that under the conditions of the experiments, thiouracil administration was followed by a "significant diminution of the sensitivity of the heart to epinephrine."—*T.H.McG.*

REVENO, W. S. Thiouracil in thyrotoxicosis. *J.A.M.A. 128* (6): 419–423 (1945).

Clinical experience with thiouracil in 32 patients is summarized as follows: 1) An initial dose of 0.6 gm. daily is usually adequate to start with and a maintenance dose after the metabolism is nearly normal varies from 0.1 to 0.3 gm. 2) Diffuse goiters usually improved in three, and toxic adenomas in nine weeks. 3) Previous treatment with iodine delayed improvement and occasionally caused an initial rise in metabolism before a fall. 4) Three patients who stopped treatment relapsed but one remained in remission. 5) The goiters usually increased in size for a few weeks, then decreased. 6) Two patients responded to thiouracil who did not respond to iodine; one patient did not respond who had responded fairly well to iodine. 7) Nausea, vomiting and cramps occurred in five patients and were controlled by decreasing the dosage.—*A.P.F.*

RIGGS, D. S., E. B. MAN, AND A. W. WINKLER. Serum iodine of euthyroid subjects treated with desiccated thyroid. *J. Clin. Investigation 24* (5): 722–731 (1945).

Four physically healthy psychiatric subjects were given desiccated thyroid substance for periods ranging from 27 to 32 weeks in doses up to 25 grains daily. Nine "non-myxedematous patients" from a general hospital clinic were given smaller doses (up to 5 grains daily) over much longer periods of time (up to two years). The precipitable and filterable fractions of serum iodine were determined by the permanganate acid ashing micromethod of Riggs and Man. In the first group of four patients the basal metabolic rate was not consistently maintained above plus 15 until 10 grains of desiccated thyroid substance or more were given daily. Similarly, the precipitable iodine of the serum, although elevated on lesser amounts, did not reach frankly abnormal values (above 8 micrograms per 100 cc.) until a dose of 10 grains per day was reached. On cessation of therapy, the serum iodine values dropped abruptly so that at the end of one week they were actually subnormal, comparable to values seen in myxedema, and did not return to normal until the end of the fifth or sixth weeks. While the variations in filtrable iodine were not as marked, they closely paralleled in kind those observed for the precipitable portion. In the patients of the second group utilizing smaller doses of desiccated thyroid substance over longer periods of time, the nature of the changes in basal metabolic rate and serum iodine were identical to those of the psychiatric group but lesser in degree. The correlation between the basal metabolic rate and the iodine of blood serum was close, but the amount of thyroid sbstance necessary to achieve a given response varied considerably from individual to individual. Attention is called to the fact that euthyroid subjects are able to tolerate considerable amounts of desiccated thyroid substance without any very striking alteration in the basal metabolic rate or the precipitable serum iodine. It is suggested that this tolerance to iodine is due to the fact that the normal thyroid gland is capable of degrading excessive amounts of hormonally active iodine to inorganic iodine.—*T.H.McG.*

TALBOT, N. B., A. M. BUTLER, AND A. H. SALTZMAN. Determination of concentration of protein-bound iodine in the serum as a measure of thyroid activity. *Am. J. Dis. Child. 69* (5): 325–326 (1945).

The authors have developed a colorimetric assay of protein-bound iodine on four cc. of serum by modifying the method of Riggs and Man. The preliminary observations are

summarized as follows: 1) the normal values for children (average, 6.5 micrograms per 100 cc.; range, 4.5 to 8.4 micrograms per 100 cc.) correspond closely to those of adults; 2) infants and children with primary hypothyroidism have abnormally low values; persons with hypothyroidism secondary to proved deficiency of the anterior lobe of the pituitary also have low values; 3) children with hypothyroidism receiving standard doses of thyroid U.S.P. (0.06 to 0.13 gm. per day) have normal values; 4) most children with idiopathic dwarfism have normal values; 5) persons with hyperthyroidism have abnormally high values; the fall in these values is parallel with the fall in the basal metabolic rate and the insensible loss of weight when thiouracil is given; and 6) when normal adults fast for six days, their iodine values fall from normal to subnormal levels. The authors conclude that the concentration of protein-bound iodine in the serum is a useful, direct index of thyroid activity which is particularly valuable for children, because the method of calculating thyroid function indirectly from the basal metabolic rate is frequently difficult to us and to interpret.—*E.C.R., Jr.*

THOMPSON, W. O. AND P. K. THOMPSON. Changes in the treatment of toxic goiter produced by thiouracil. *Proc. Central Soc. Clin. Res. 17:* 10–12 (1944).

From the available data it appears probable that in patients with toxic goiter who are not hypersensitive to thiouracil and who do not develop serious toxic reactions, the administration of thiouracil in proper doses will cause a reduction in BMR to within normal limits and maintain it there for six months or in some cases indefinitely. It appears probable that toxic goiter may be treated by the administration of thiouracil alone. In patients who have the disease in a very severe form and who cannot be prepared for surgical procedure by the various measures commonly employed and who are not hypersensitive to the drug, long periods of hospitalization before operation may be avoided by the administration of thiouracil.—*Courtesy Biol. Absts.*

WALLER, R. K. AND H. A. CHARIPPER. Electrocardiographic observations in normal, thyroidectomized and thiourea-treated rats. *Am. J. M. Sc. 210* (4): 443–452 (1945).

A method was evolved for determining the electrocardiogram of the rat, and the normal pattern established. Patterns were then obtained at suitable time intervals from eight thyroidectomized and from eight thiourea-treated rats. The changes after thyroidectomy simulated in all respects changes seen in human cases of myxedema (lowering of heart rate with increased conduction time and lessened amplitude of all positive waves). These changes were more pronounced in animals thyroidectomized six months before than in those operated three weeks before. Treatment of normal rats for three weeks with thiourea produced marked slowing of the heart rate with increased conduction time and lowered amplitude of the T waves. However, there was a striking tendency to increase the voltage of the R waves, in complete contrast to the expected myxedematous changes. Although there was no consistent shift in axis deviation after thyroidectomy, there was a definite shift to the right in the majority of the thiourea-treated animals. The authors conclude that the more complete myxedema-like response obtained after thiourea treatment as compared to that elicited following thyroidectomy lends further substantiation to the previously-proposed thesis of an extra-thyroidal production of thyroxin.—*E.C.R., Jr.*

WILLIAMS, R. H. AND H. M. CLUTE. Thiouracil in the treatment of thyrotoxicosis. *J.A.M.A. 128* (2): 65–69 (1945).

One hundred fifty-two cases of thyrotoxicosis treated with thiouracil are analyzed. The safest effective dosage proved to be 0.6 gm. daily for two weeks, then 0.3 or 0.4 gm. until the metabolism was normal, then 0.2 gm. for maintenance. The metabolism usually reached normal in four to six weeks and remained there as long as the drug was continued. Benign exophthalmos decreased but malignant exophthalmos increased unless thyroid extract was also given. Previous treatment with iodine delayed the response to thiouracil by about four weeks. In most patients there was an eventual reduction in the size of the gland. Thyrotoxic manifestations during thyroidectomy were distinctly less severe in the cases treated with thiouracil than in a similar group treated with iodide. Although the thiouracil treated glands tended to bleed more freely, the addition of iodine treatment for the last two or three weeks before operation reduced this hazard in part. In glands so treated there was less hyperplasia and more colloid microscopically. Sixteen of the 152 patients developed untoward reactions to thiouracil. These occurred mostly in the first 5 weeks and in the patients given larger doses. Most patients were able to continue the drug in reduced amounts.—*A.P.F.*

WINKLER, A. W., D. S. RIGGS, AND E. B. MAN. Serum iodine in hypothyroidism before and during thyroid therapy. *J. Clin. Investigation 24* (5): 732–741 (1945).

Values for the iodine of the blood serum were determined in 30 patients with hypothyroidism before and after adequate treatment (one to three grains daily) with desiccated thyroid substance. The average serum iodine in the "fore" and treatment periods was 1.3 and 4.8 micrograms per 100 cc., respectively. The relationship between the serum iodine and the daily dose of desiccated thyroid substance appeared to be linear within the limits of zero to two grains per day. As a rule, a one grain increase in the daily dose produced an increase in serum iodine of approximately two micrograms per 100 cc. As soon as all of the clinical manifestations of the hypothyroidism were relieved, the blood serum iodine was invariably within normal limits. The authors concluded that serum iodine is not only a valuable aid in diagnosis, but also equally useful in determining the adequacy of therapy.—*T.H.McG.*

WOSIKA, P. H. AND L. BRAUN. Fatal agranulocytosis occurring during treatment with thiouracil. *J. Lab. &. Clin. Med. 30* (9): 779–783 (1945).

The authors report the case of a 50 year old woman with nodular goitre, who died with the syndrome of agranulocytic angina on the 76th day after treatment with thiouracil was begun. She received a total of 29.4 gm. of drug; she initially took 0.6 gm. daily for 31 days, but at the time of the reaction had been using 0.1 gm. daily for ten days. The authors summarize salient features, such as dosage and duration of treatment, in eight other reported cases of agranulocytosis, due to thiouracil, four of which ended fatally. They emphasize the point that the most serious reactions within the bone marrow have occurred between the fifth and eighth weeks of treatment.—*T.H.McG.*